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THE OUTLOOK FOR THE EVENTUAL CONTROL OF LEUKEMIA*

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IN any attempt to discuss the outlook for the eventual control of leukemia, it may as well be conceded that as of today efforts have been pitifully disappointing. Whether all this is due entirely to the inherent difficulties of the problem or to insufficient application of all available resources is debatable. In any event, to dismiss leukemia as hopeless is far from accurate, since many potential accomplishments are on the horizon, and at least a few important steps have already been made.

What can be done to further the cause against what is admittedly the foremost problem in hematology? There is surely no easy way, but perhaps one can dramatize leukemia less and study its fundamentals more. The frenetic search for new therapeutic agents, often used more by accident than design, might conceivably give way to a more sober approach. Studies of the chemistry and physiology of the white blood cells, their enzymatic constituents, their hormonal control and their growth properties in culture and on exposure to harmful agents — these offer many opportunities for significant research. It is, of course, possible that at any moment some lucky (or "prepared") person will come upon a cure for the disease before the cause is found. However, the odds are very much against this, although perhaps one should not be so pessimistic here in Boston, where liver was found to cure — for all practical purposes — a previously fatal illness, whose fundamental causes in 1926 were quite obscure.

Since at the moment little is known about the control of leukemia, it may be best to discuss some of the fundamentals of this disease, and to review very briefly what little information on the subject is available.

DEFINITIONS

Leukemia is one form of generalized white-cell-system proliferation. Various types of proliferative processes and several different white-cell systems may be identified. The white cells are derived from four different sources: the bone marrow, the lymphoid system, the reticuloendothelial system, and the system of plasma cells (plasmocytes). These "systems" are all diffusely scattered throughout the body, and all produce leukocytes, some of which eventually find their way into the blood. The white blood cells corresponding to these systems are shown in Table 1.

The various white-cell systems are subject to proliferative activity, which is commonly benign and reversible. Such activity is usally in response to a well defined stimulatory agent, the most common being an infectious process. Trauma, hemorrhage, stress and "toxic" causes may also result in a rapid, apparently purposeful and benign proliferation, which ceases when the causative agent or factor has departed or been conquered. Certain agents and conditions evoke specific types of leukocytic proliferation, of which the granulocytic variety is by far the most common. Most infections, especially those of the pyogenic type, are associated with hyperplasia of the bone-marrow leukocytes and an increase of the polymorphonuclear leukocytes in the blood. This also occurs in hemorrhage, trauma and stress. The granulocytic response is usually associated with a reciprocal lymphocytic effect — that is, a great reduction in lymphocytes usually occurs simultaneously with the granulocytosis. An associated and quite mysterious effect is the extreme reduction and often complete absence of eosinophils from the blood.

TABLE 1. *Derivation of White Cells from Body Systems.*

SYSTEM	TYPE OF CELLS
Bone marrow (granulocytes)	Polymorphonuclear leukocytes
Lymphoid system	Lymphocytes
Reticuloendothelial system	Monocytes
Plasma-cell system	Plasma cells — plasmocytes

Other disturbances evoke lymphocytic, monocytic and plasmocytic responses. The last are ordinarily seen with chronic infectious or immunologic reactions. An infectious process, probably viral, that evokes a considerable and often peculiar proliferation of lymphocytic tissue is that of "infectious mononu-

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cleosis." Here, there is an extreme degree of lymphocytosis, with the production of bizarre lymphocytes, and a seemingly invasive tendency, which may be noted in both spleen and lymph nodes. Mitotic figures are fairly numerous, and the capsule of the lymph node is often invaded by the proliferating cells.

For the most part, however, the benign proliferative disturbances of the white-cell systems have the following common features: a well defined cause; orderly growth, which is noninvasive; and reversibility. These characteristics are quite in contrast with the malignant leukocytic proliferations, in which a well defined cause is hardly ever discernible, the growth is disorderly, invasive and purposeless, and complete reversibility, instead of being common, is unusual.

In general, two types of malignant leukocytic proliferations may be identified: one generalized, and the other localized. Since Virchow's time the generalized type has been known as "leukemia," although in many cases this term is not strictly accurate — that is, there is no "white blood." There is no real distinction between leukemic and aleukemic cases of leukemia, the tissue histology being identical. Leukemia, according to modern definition, represents a generalized neoplastic proliferation of one of the white-cell systems. It may or may not be associated with a high white-cell count. The localized proliferations have gone by a variety of designations, including "lymphoma," but I have preferred for them the term "leukosarcoma,"[1] which implies a malignant, sarcomatous neoplasm of the white-cell series and can be contrasted with "leukemia." The malignant white-cell proliferations are classified in Table 2.

TABLE 2. *Malignant White-Cell Proliferations.*

GENERALIZED PROLIFERATION (LEUKEMIA)	LOCALIZED PROLIFERATION (LEUKOSARCOMA)
Granulocytic	Granulosarcoma (chloroma)
Lymphocytic	Lymphosarcoma
Monocytic	Reticulum-cell sarcoma
	Hodgkin's disease
	"Eosinophilic granuloma of bone"
Plasmocytic (multiple myeloma)	Plasmocytoma (solitary myeloma)

It should be noted that the terms granulocytic, lymphocytic, monocytic and plasmocytic are used for the leukemias instead of the more common designations of myelogenous, lymphatic, monocytic and multiple myeloma. This represents an attempt at consistency, and is in line with the recommendations of the Committee on Nomenclature of the American Society of Clinical Pathologists.[2] Furthermore, instead of the term "lymphoma," which means very little and is often inaccurate, the white-cell neoplasms are classified more or less in parallel with the leukemias. Although some may disagree with the designation of "plasmocytic leukemia" for multiple myeloma, it is quite evident that this disease represents a generalized malignant proliferation of plasma cells throughout the entire body, notably in bone marrow. This is therefore as much a "leukemia" as chronic lymphocytic leukemia. Hodgkin's disease, also more or less controversial in nature, is classified with the reticulum-cell proliferations, a view that is now generally accepted. In contrast with the leukosarcomas, or the solid white-cell neoplasms, which probably begin "unicentrically" (that is, in one area, later becoming generalized), the leukemias seem to be generalized from the start. In this, they resemble the benign infectious proliferations, in which, as the result of a well defined cause, a generalized white-cell proliferation takes place. Is it possible that leukemia is also the result of factors whose nature is at present obscure?

The various neoplastic processes, whether generalized or localized, are subject to varying degrees of growth potentiality. In this, they differ in no wise from other neoplasms, which have often been graded on a numerical scale of malignancy. Each case of leukemia or leukosarcoma seems to have its own "predetermined" standard of growth potential: it is extremely rapid in some and relatively slow in others. The most rapidly growing and most invasive cases are composed almost exclusively of primitive cells (blast forms and even their precursors), with little if any tendency to differentiation, and show many mitotic figures. On the other hand, the most slowly growing forms are made up largely of mature cells, primitive cells and mitotic figures being difficult to find. This difference in growth potentiality is all-important, from the standpoint not only of prognosis but also of therapy. The clinical term "acute" is used for the most rapidly developing forms of leukemia; subacute and chronic forms are also recognized. A similar situation holds true for the solid tumors, the leukosarcomas. Thus, lymphosarcoma is as variable a disorder as lymphocytic leukemia. By careful evaluation of a biopsy preparation acute, subacute and chronic forms of lymphosarcoma may be distinguished. This simple classification for growth potentiality in leukosarcoma appears to be little used, most pathologists seemingly being content with making the diagnosis of lymphosarcoma or reticulum-cell sarcoma.

Another feature distinguishing the leukocytic from other proliferations is the frequency with which the circulating blood shows "samples" of the proliferating tissue. It should be recognized that leukemia is a proliferation of the tissue cells, and not of the blood leukocytes. Thus, the blood may or may not reflect what is going on in the tissues. Although in perhaps half the cases of leukemia, the leukocyte count is higher than normal, and more or less primitive cells are present in the blood, about half the patients have leukocyte counts that are either normal or at leukopenic levels. Thus they are not "leukemic" in the sense in which Virchow used the term.

For these cases, the term "aleukemic" is ordinarily used, even though "aleukemic leukemia" is a contradiction in terms. Some cases of this type are so completely aleukemic that it may take either a bone-marrow aspiration or a lymph-node biopsy to reveal the true nature of the process. Of the solid, leukocytic neoplasms, the great majority are aleukemic, as might be expected since they exist at their inception in one or a few sites only. However, when they become generalized, a leukemic picture frequently supervenes, particularly in granulosarcoma (chloroma) and often in lymphosarcoma and reticulum-cell sarcoma. Localized plasmocytoma, when it becomes generalized, shows the typical "aleukemic" features of multiple myeloma, in which, although the bone marrow is crowded with plasma cells, the blood contains none or very few.

Incidence

It appears that leukemia is on the increase. Although impressions obtained from reviews of clinical material may be faulty, a few carefully controlled observations indicate that the incidence of leukemia is increasing, not only as a diagnosis but also as an actuality. Thus, Sacks and Seeman,[3] in 1947, in analyzing the crude mortality rate from leukemia in the United States Death Registration areas, found that a sharp increase had begun about 1922 and had continued to the last date of their study — namely, 1944. The crude mortality rate had risen from 1.0 per 100,000 population in 1900 to 4.3 per 100,000 in 1944, although much of this rise must be considered more apparent than real, since diagnostic methods before 1920 were by no means well developed. Even from 1920 to about 1935 (the latter date coinciding with a greater interest in the leukemic problem and a wider use of bone-marrow studies), the diagnosis of leukemia often left much to be desired. The continued rise in the slope of the curve from 1939 to 1944 would be difficult to explain on the basis of better diagnosis alone. In any event, each year since 1940, more than 5000 persons in the United States have died of leukemia, and in the last few years, the deaths have risen to over 6000.

A more recent study from Scotland — by Gauld, Innes and Robson[4] — of 647 cases indicates an approximate doubling of the incidence of admissions for leukemia to several large general hospitals in Scotland during the period of 1938–1951, when diagnostic methods were approximately standard. There was 1 case of leukemia in about 2000 hospital admissions in 1938–40, and about 1 case in 1000 admissions ten to twelve years later. The ratios of the types encountered were approximately as follows: chronic lymphocytic, 6 cases; chronic granulocytic, 5 cases; acute lymphocytic, 4 cases; and acute granulocytic, 2 cases. The relatively large number of cases of the chronic lymphocytic type may be explained by the common finding of these cases in the older age group on routine blood examinations during a general checkup. It is of further interest that the relatively benign chronic cases outnumbered the more widely publicized acute ones by about 2:1. A similar incidence was found in this country.[5]

The acute cases occur in any age group, but most of the acute cases in childhood are of the lymphocytic variety, granulocytic and monocytic cases in patients under twelve years of age being quite exceptional. Acute granulocytic leukemia occurs about equally in almost every age group. Some of these cases are of the so-called myelomonocytic variety, in which a large number of the circulating white blood cells are monocytes. Pure monocytic leukemia is unusual, occurring in about 5 per cent of all acute cases.

If an actual increase in leukemia has occurred in the last two decades, what can it be due to? Is it possible that the increasing complexity of present-day civilization, with its numerous chemical and radiologic contacts, has something to do with the increase? There can be no doubt that people are surrounded by all kinds of possibly harmful chemicals and medications. In the air are exhaust gases from automobiles and the fumes of tars from the roads. Potent chemicals are imbibed as medications, and many of them are absorbed in the form of ointments and lotions. Even foods may contain not entirely inert chemicals for preservative purposes. X-rays are used more and more frequently.

Possible Etiologic Factors

Of the various possible causes of leukemia, only one — namely, that of irradiation with x-rays — has been reasonably well documented from both clinical and experimental observations. In radiologists the incidence of leukemia has been found to be approximately eight times that in a comparable group of physicians in other fields.[6-8] This has been demonstrated in at least two separately conducted studies in this country and must be considered as far beyond the possibilities of chance observation. Frequent and prolonged x-ray exposure, with perhaps some degree of laxity in protection, almost certainly favors the development of leukemia. A single high-dosage exposure of x-rays and gamma radiation may also be leukemogenic, as demonstrated in the studies made after the atomic-bomb explosions in Hiroshima and Nagasaki. Amano[9] has noted that of those surviving the blast, the incidence of leukemia was thirteen times higher in the epicenter of the blasted area at Hiroshima than at the periphery.[10] In the general area of bombed Hiroshima, the incidence of leukemia was approximately eight times that of Japan in general. The high incidence of leukemia was noted one to four years after the atomic explosion. Thus, in persons in whom some degree of bone-marrow injury develops after irradiation, the incidence of leukemia may be extraordinarily high.

Such massive exposure to x-rays, either acutely or over a long period, is rarely seen in clinical practice, but there can be no question that x-ray exposure in the general population is far higher that it was years ago. Many persons, particularly those who have frequent examinations, are subjected to often prolonged fluoroscopic studies, during which the total dosage of x-rays may be considerable. Many patients with chronic dermatologic disorders are treated with prolonged x-ray therapy, and although this is applied superficially, one cannot be certain how potentially dangerous it is. X-ray therapy for possible hyperplasia of the thymus, a method practiced not too long ago before tonsillectomy, may not be without danger. On one occasion several years ago, I observed 3 children with acute leukemia within a period of a month, all of whom had been given x-ray therapy for hyperplasia of the thymus discovered on routine roentgenograms of the chest before projected tonsillectomy.

Another method for x-ray exposure is the use of shoe-fitting machines equipped with fluoroscopic devices. It has been calculated that some of these machines may emit as many as 4.5 to 23 r during a prolonged shoe fitting.[11] In the treatment of chronic granulocytic leukemia, the use of x-ray therapy, although valuable, may be conducive to the development of the "myeloblast crisis" occurring some years later. In the treatment of polycythemia vera, the use of radioactive phosphorus, which produces excellent remissions, may not be altogether harmless, in that the incidence of acute leukemia in these cases seems to be distinctly greater than that in cases of polycythemia treated only with venesection.[12, 13]

Although these examples of the possible relation of x-ray exposure to the subsequent development of leukemia are undoubtedly speculative, there seems to be no doubt regarding the leukemogenic effect of prolonged x-ray exposure or of an extremely large single dose of x-rays or gamma rays. Little is known about the mechanism by which x-rays may induce leukemia. One may speculate that destruction of the bone marrow, an undoubted x-ray effect, may be followed by a bizarre type of leukocytic proliferation, which eventually becomes neoplastic and thus leukemic. A more direct effect of x-rays might be to interfere with cell growth, altering chromosomes and mitoses and thus leading to abnormal cell growth or to highly abnormal mutation forms. It is also conceivable that x-ray injury acts as a "trigger mechanism" allowing a previous occult or latent abnormality to develop in full (this possibility is discussed below, under Viruses).

Chemicals

Benzene. Since the time of Selling's[14] experiments with benzene it has been known that this chemical may cause severe injury to the bone marrow and thus result in varying degrees of aplasia, with a reduction in all or some of the cellular constituents derived from the marrow. That this and the related chemicals toluol and xylol may under certain circumstances induce leukemia has been suggested by increasing numbers of observers in the last several years. Thus, Lignac,[15] in 1932, induced various types of leukocytic proliferation in mice by prolonged benzene administration. Mallory, Gall and Brickley[16] reviewed the evidence for the relation of chronic benzene exposure to leukemia in a classic article written in 1939. From their studies of 19 cases with prolonged exposure to benzene in which histologic material was available, they concluded: "The evidence that chronic exposure to benzene produces leucemia in human beings is still incomplete but it is accumulating at a rate and to a volume which command serious attention." Since then, several studies have emphasized the same conclusion. In my own experience, the leukemia found is usually subacute. Cases have been observed in automobile mechanics exposed for years to various types of gases and oils, in persons working with oils and greases and using benzene and xylene for "cleaning up" and in those working with paint removers containing aromatic solvents and the like. Whether or not the leukemia is actually induced by the chemical is always in question in a given case, even when the exposure is clear-cut and quite prolonged. Moeschlin[17] has listed the following conditions under which one can accept chemical exposure as the cause of a given case of leukemia: the patient must have been in intimate contact with the chemical for a period of at least three and preferably five or more years, and must give actual evidence or at least strong probability that a relatively high concentration of chemical was present (poor ventilation, small rooms and possible blood disorders in other workers).

Carcinogenic hydrocarbons. That tars are carcinogenic is well known. A few experiments are on record indicating that the application of certain hydrocarbons to the skin of mice is followed by a high incidence of leukemia.[18] More recently, Shay[19] induced a rare granulocytic type of leukemia (chloroleukemia) in rats of a relatively leukemia-free strain by the gastric instillation of methyl-cholanthrene, a petroleum hydrocarbon. It was then possible to transfer the leukemia from rat to rat, provided the transfer was done shortly after birth of the animal.

In view of the experimental data with both the aromatic solvents and the carcinogenic tars, it is valid to speculate on the possibility that either long-continued exposure to certain chemicals or a short violent exposure, or perhaps inherent or induced sensitivity to certain chemicals, is productive of leukemia. In this chemical age, exposures are multitudinous, and it is possible that some of them have etiologic significance in certain susceptible persons. One may even question the benignity of high-potency

vitamin preparations and hormones, often used in massive doses.

Viruses

A type of leukemia occurring in fowl (avian erythromyeloblastic leukosis) is caused by a virus, which has been isolated, grown, photographed and passed from animal to animal. Its etiology has been recognized since 1907, and the causative agent is present in the plasma of leukotic chicks.[20] The leukemia induced by the cell-free, virus-containing material is a highly malignant "acute" process characterized by the occurrence in the blood of primitive nucleated red cells or primitive granulocytes (myeloblasts) or both,[21] thus presenting a picture not unlike that described in the di Guglielmo syndrome of erythroleukemia.

The well documented character of this virus-induced leukemia has naturally led to search for viruses in other animal leukemias, but generally without success, and for a long while the possible virus etiology of leukemia lay dormant, especially since more productive work on carcinogenesis by chemicals, hormones and radiation held the spotlight. Recently, however, largely through the writings of Gross,[22, 23] the subject has been reopened. Gross inoculated mice of the C3H strain, in which leukemia is rare, with extracts, some of which were cell free, of leukemic tissues of AK mice, in which leukemia is very common. If the inoculations were made in mice that were several days or weeks old, leukemia was not induced, but when they were made within a few hours after birth, leukemia developed in a large proportion of the C3H animals. Leukemic tumors developed in some of the animals near the site of the injection within two or three weeks, but in many cases, the disorder did not appear until the mice had reached "middle age" — that is, twelve to twenty-seven months of age.

These data are reminiscent of previous work with the Bittner milk factor[24] in which breast tumors were ultimately produced in mice fed milk shortly after birth from carcinoma-bearing foster mothers. The virus nature of the milk factor is generally recognized. Since the "spontaneous" leukemia of the AK strain not only could be transmitted to C3H mice but also, apparently, could lie dormant in the C3H strain for months at a time without causing leukemia, it was natural to suppose that a virus might be responsible. That the leukemia could be transferred from one C3H mouse to another only if the inoculations were made shortly after birth led to the supposition that mouse leukemia was transmitted from one generation to another and to the concept of a "vertical"* transmission of leukemia. The high incidence of leukemia in AK mice, generally assumed to be on a hereditary or genetic basis, was regarded by Gross as due to intra-uterine viral transmission to offspring, the virus perhaps lying dormant for many months at a time without causing any apparent injury to the host. If the animal with latent virus gave birth during this period, and before leukemia developed, the leukemic virus might be transferred in this "hidden" fashion to the offspring, in which leukemia might develop although the mother died of some intercurrent disease. The agent might lie dormant within the host until for some reason activation occurred, with the result that there was a rapid neoplastic proliferation of the cells harboring it, resulting in leukemia. A more recent finding by Gross[25] is the presence of a carcinogenic material in the cell-free supernatants of leukemic tissue, centrifugated at high speed. This may indicate a relation between cancer and leukemia. It has been shown that a family history of cancer is far more common in cases of leukemia than in nonleukemic persons.

Gross's concepts have caused considerable interest but require confirmation, particularly at the hands of virologists, before they can be accepted. To prove these assumptions in human beings would require better methods of virus investigation, and careful studies of family trees for at least two hundred or three hundred years. In rapidly breeding mice, such information is not only more readily obtainable but also developed under controlled conditions.

Hormonal Abnormalities

Current studies on the influence of hormonal activities on various bodily processes have resulted in an increasing interest in the possibility that the hormones are implicated in leukemic development. The reciprocal or inhibitory relation of the adrenocortical extract, cortisone, to lymphoid, splenic and thymic tissue is well known, and there is some evidence of a simultaneous myelostimulatory effect.[26] A possible reciprocal relation between the lymphocytic and myelocytic tissues may be present, and it has been proposed that an "equilibrium disturbance" between these two types of tissues (Ziegler) might be responsible for the development of lymphocytic or granulocytic leukemia, as the case may be.[27] That lymphocytic and granulocytic leukemia may be reciprocally related has been proposed, not only on clinical grounds but also on the basis of studies with urinary extracts from patients with leukemia. Miller and Turner[28] have isolated "lymphokentric acid" from patients with lymphocytic and "myelokentric acid" from those with granulocytic leukemia. They hypothesized that an excess of lymphokentric acid might result in lymphocytic leukemia by outbalancing myelokentric acid. More recently, these workers have postulated a relation of these chemicals to the steroid hormones[29] and thus have brought them in line with recent hormonal studies.

*Not "horizontal," as in ordinary infectious spread.

It may well be that hormonal factors are operative in the different types of leukemia and related disturbances, but their exact function is not clear, and they may indeed have a purely secondary role to some more fundamental agent. To classify leukemia among the "general adaptative syndromes," as some have done,[30] seems premature.

Heredity

As already noted, leukemia develops in 80 to 90 per cent of the AK pure-bred mouse strain. That this is a hereditary disturbance, based on the passage of an abnormal gene, had been quite generally accepted until the recent investigations of Gross, as noted above. Nevertheless, since the viral theory is by no means proved, the factor of heredity must continue to be studied. Videbaek[31] lists the literature of familial leukemia, as well as of a personally studied group of 209 patients and their families, and of 200 control probands. Videbaek found that leukemia, when it occurred in siblings, developed at about the same age, making it unlikely that it was a matter of "fortuitous coincidence." The occurrence of several cases of leukemia in the same family was much too frequent to be explained by coincidence. The familial incidence of leukemia, at least 8 per cent, could be compared with an incidence of 0.5 per cent in the control material — certainly, far removed from the coincidental. Videbaek concluded that leukemia was a matter of chromosomal inheritance, not of leukemia as such, but of an inherited predisposition. In further studies, he found that there was a much higher incidence of cancer in the relatives of patients with leukemia than in the controls, indicating the possibility of the inheritance of a gene common to all the different forms of neoplastic proliferation. The risk of cancer in near relatives of a patient with leukemia might be as high as 50 per cent, indicating that cancer should be carefully sought in any vague complaint occurring in the relatives.

Like many others, Videbaek believes that the leukemic type of inheritance is one of "predisposition" and that some other environmental agent is essential. In the presence of the appropriate "soil," the hypothetical agent results in leukemia. Thus, the statement ordinarily made that leukemia is not hereditary must be questioned. A history of cancer and of leukemia in the family should be searched for carefully in every patient seen, thus building up adequate control and disease observations.

Other Possible Causes

Disturbance of leukocytic elimination. Bierman[32] recently revived the concept that the fundamental disturbance in leukemia might be a failure to eliminate cells normally produced. The retention of white cells by the lungs of leukemic patients was shown, as compared with normal controls.

Deficiency disease. The idea of leukemia as a deficiency disease is based on the vague hope that what was done with pernicious anemia and liver might be carried out with leukemia. Unfortunately, there is little to justify this possibility.

Summary

In conclusion, one may summarize the outstanding possibilities of the etiology of leukemia as follows:

Myelotoxic agents, such as x-rays and chemicals, if they produce sufficient destruction, may eventually lead to an abnormal, leukemic proliferation, at least in some (hereditarily predisposed?) persons.

Viruses, latent perhaps for years and transmitted "vertically," — that is, from one parent or the other to offspring, — may result in leukemia either by their own activities or through the mediation of such activators as x-rays and chemicals.

This is about all one can say at the present writing of the causation of leukemia, but it represents at least a beginning, as well as an advance away from the often repeated phrase that "nothing is known of the causation of leukemia."

Recent Advances in Therapy

Thus far, in the attempt to find what can be done about leukemia, etiology has been emphasized, for if it is known what causes a given condition one can perhaps do something about it. On occasion, however, therapy has outstripped knowledge of pathogenesis, and to some extent this is true of leukemia. A brief review of therapeutic methods is therefore given.

Except in the acute cases x-ray therapy for leukemias has been standard procedure for years. In acute leukemia, unfortunately, it usually makes the situation worse, and in the continued therapy of the chronic case, its action has often left much to be desired. X-ray therapy is furthermore nonspecific, and requires the services of highly skilled specialists and expensive equipment. With the development of the newer chemotherapeutic methods, some of them highly effective, this therapeutic modality may be on its way out in the treatment of the white-cell proliferative diseases. The radioactive isotopes, from which so much was once expected, have been disappointing. In the acute cases they have no value, and their only value in the chronic ones is in the granulocytic variety, in which they are usually no better than x-rays. Polycythemia vera, which may be more or less closely related to chronic granulocytic leukemia, is, to be sure, affected favorably, but there is some question about possible aftereffects such as acute leukemia. On the other hand, chemotherapeutic methods have evolved rapidly in the last decade, and show distinct promise, especially in selective therapy.

Although Fowler's solution was introduced in the 1860's, and benzene in the 1900's, chemotherapeutic methods for the treatment of leukemia and related states were not used to any great extent until the war years of the 1940's, when nitrogen mustard was introduced.[33] It was soon apparent that the latter material was often highly beneficial in Hodgkin's disease, especially when the process was generalized and systemic symptoms were present.[34] In some cases of generalized lymphosarcomatosis, its use was often attended with spectacular and long-sustained remissions. However, in the leukemias themselves it was of no particular value. On the other hand, urethane was found to be helpful in maintaining the x-ray-induced remission of chronic granulocytic leukemia and in the therapy of multiple myeloma.[1] A number of other chemicals were then introduced, of which the most important in my judgment have been aminopterin, triethylene melamine (TEM) and the hormones, ACTH and cortisone.

Aminopterin and hormones. Aminopterin is the amino acid analogue* of folic acid.[35, 36] It is particularly useful in the acute leukemia of childhood, youth and perhaps early adulthood; in these age groups, most of the cases are of the lymphocytic variety. In adults over thirty years of age its toxic effects are so marked and its beneficial effects so uncommon that its use is questionable. When it is given as the sole therapeutic agent in children and young adults, complete remissions (of clinical, peripheral-blood and bone-marrow findings) may be obtained in approximately 50 per cent of the cases. In combination with large doses of ACTH, it produces remissions even more frequently, especially in children with the lymphocytic type. In an eighteen-month period, complete remissions were obtained in 25 of 26 cases of acute lymphocytic leukemia in children.[37] During the same period, only 2 cases of acute granulocytic leukemia were encountered in children, and these failed to respond to this therapy. The remissions in childhood leukemia, both leukemic and aleukemic, appeared within one to six weeks and were maintained for periods of four weeks to two years. Second, third and even fourth remissions have occurred, but each successive one is shorter and more difficult to produce. A simple clinical remission, in which the patient felt and looked quite well, was easiest to obtain, even in some adults. A hematologic remission, with completely normal peripheral blood, was also relatively easy of attainment in children, but less so in adults. It is difficult to achieve an almost completely normal bone marrow — that is, one containing less than 5 per cent abnormal primitive cells — unless active and persistent therapy is given; this is particularly true of the second and third relapses. The necessity for examining the bone marrow from time to time during therapy has become quite clear. Unless the marrow is almost entirely cleared of primitive abnormal cells, relapses in the leukemic state develop quite rapidly. The simultaneous administration of ACTH or cortisone seems, first, to enhance the effects of aminopterin, secondly, to increase greatly the chances for a remission, thirdly, to reduce to a large extent or even completely the ordinarily noted "toxic" reactions to aminopterin, fourthly, to decrease the bleeding tendency common in acute leukemia, especially with aminopterin therapy, and finally to result in a myelostimulatory effect when bone-marrow aplasia has been induced by aminopterin. ACTH and cortisone alone result in remissions in children in at least 50 per cent of the cases,[20] but the remissions are short lived and the relapses difficult to treat. The combined use of ACTH and aminopterin has been remarkable in obtaining a temporary beneficial effect. Unfortunately, even with the best of methods and the best of results, the time comes in every case when it is no longer possible to reverse the leukemic process and the inevitable end result occurs.

It has been found that maintenance ACTH or cortisone therapy is advisable, together with either small doses of aminopterin twice weekly or occasional short courses of aminopterin. The judgment of the exact type of maintenance therapy is difficult, depending in large measure upon the blood and principally upon the marrow picture.

Triethylene melamine (TEM). This chemical is by all odds one of the most potent so far introduced[38] for therapeutic purposes and, if used with appropriate caution, one of the most useful. In contrast with aminopterin, which has a relatively narrow range of usage, TEM may be considered a "broad-spectrum" chemotherapeutic agent. Thus, it may be of value in many cases of Hodgkin's disease, chronic lymphocytic leukemia, chronic granulocytic leukemia and lymphosarcoma.[39] Its potency as an anticellular agent is extraordinary. For this reason, it should be given with great caution, and its dosage in adults should never be greater than 2.5 mg. A test dose is worth while, since in an occasional patient severe reactions, generalized and hematologic, develop. In the first course of therapy the dose should be no greater than 2.5 mg. given three times in the first week and twice in the second. To avoid contact with food, the drug is always administered an hour before breakfast.

The greatest value of the drug appears to be in chronic lymphocytic leukemia and lymphosarcoma. Provided a serious bone-marrow hypoplasia does not ensue, a complete clinical, hematologic and bone-marrow remission may be obtained in about 6 of 10 cases of chronic lymphocytic leukemia. The remission may be maintained for long periods with the use of a dose of 2.5 mg. at intervals of ten to fifteen days. Lymphosarcoma, whether localized or generalized, is often greatly benefited and in some

*An analogue is a chemical substance that is almost identical chemically with another substance but may have the opposite action metabolically.

cases kept under complete control with maintenance therapy given at intervals of five to fifteen days. White-cell counts and platelet estimations (from blood smears) are performed at each visit, and the drug is discontinued for a month to three months if leukopenia or thrombocytopenia occurs. In Hodgkin's disease, TEM has been disappointing for maintenance therapy, although in some cases it seems to be quite effective for lengthy periods. Chronic granulocytic leukemia is still best treated with x-ray therapy over the spleen and with urethane for maintenance, although there is increasing indication that the new chemical GT41, or myleran,[40, 41] may be more effective than either of these two methods.*

Lessons Learned from the Use of Newer Chemotherapeutic Agents

It is possible at this point, approximately ten years after the first therapeutic efforts with these potent chemical agents, to summarize briefly what has been learned from their use.

In the first place leukemia, even of the acute type, represents a possibly reversible disease. It is true that the reversal may be only for short periods, but the mere fact that it is possible not only to stop a rapidly growing, highly invasive growth process but also to restore the normal, orderly growth process in lymphoid and marrow tissues is the most important lesson one can gain from these studies. For, if the proliferation can be stopped for a few months, perhaps it can be stopped for a few years; if it can be stopped for a few years, perhaps it can be stopped for a number of years. Thus, conceivably, one might in the end be left with a disease that was perhaps not curable but *controllable;* it would matter little whether the disease was cured, so long as the patient remained clinically in good health.

Secondly, the antileukemic agents possess a certain degree of specificity. Thus aminopterin is most useful in the acute lymphocytic leukemia of childhood, TEM in chronic lymphocytic leukemia and lymphosarcoma, and myleran in chronic granulocytic leukemia. With the host of chemicals that it is possible to synthesize, the possibilities of specific agents for specific diseases seem to be good.

Thirdly, the antileukemic agents may act through entirely different cellular mechanisms. Thus aminopterin owes its activity to its folic acid antagonism, ACTH probably to its lymphocytic inhibitory nature, and 6-mercaptopurine,[42] one of the newer agents, to its activity as an antagonist to nucleic acid production. With increasing knowledge of cellular chemistry and of enzyme systems, it is highly probable that other specific chemical and enzymatic antagonists will be evolved.

Finally, the antileukemic agents, except for ACTH and cortisone, have one feature in common — that is, their myelotoxicity. This holds true not only for aminopterin, TEM, HN_2, urethane, myleran and 6-mercaptopurine but also for x-rays and radioactivity in general. Thus, it seems that for an agent to be of value therapeutically, it must also have marked myelotoxic properties. What this means is not entirely clear. One way of looking at the problem is as follows: the chemical must destroy all the abnormal cells; in so doing, the marrow cells are also destroyed; when growth returns, normal growth returns first. Later, abnormal growth reappears and the process is repeated. If this were so, every myelotoxic agent should act in a similar manner, but it is not so, since a certain degree of specificity is observed. In any event, it seems that to obtain a good therapeutic result in many cases, it is necessary to go the point of serious bone-marrow injury.

PROGNOSIS

There are indications that leukemia, instead of being a hopeless disease, may eventually be put under control. Here both the investigators in their laboratories and the practicing physician could be of help. Investigators have outstanding opportunities, which may be listed as follows: examination of the cultural, chemical and enzymatic characteristics of normal and leukemic cells; study of possible etiologic agents, with particular reference to the experimental production of leukemia by chemicals, x-rays and viruses; and continued search for specific chemotherapeutic agents. It is of course possible (as in other conditions) that agents capable of causing complete and sustained reversal of various leukemic states will be developed long before the cause of the disease is known or the reason for the therapeutic action is discovered.

The practicing physician also has his opportunities. Thus, his knowledge of the family might be useful in working out family histories of cancer and leukemia and their possible inter-relations; his intimate knowledge of the patient might help to ferret out possible chemical or other etiologic factors; his position in the vanguard of medical practice gives him the opportunity to limit the widespread use of many powerful chemicals, drugs, hormones and other therapeutic agents. In particular, the general practitioner should be on the alert regarding the commonly used dermatologic therapeutic agents such as tars, phenols, chrysarobin, and x-rays. He should keep in mind the vulnerability of those of his patients who come in frequent contact with such chemicals as benzene, rubber cement, paint remover, arsenicals and insecticides. Such persons might be asked to have occasional blood counts, and if these are at all abnormal, their occupational duties might be curtailed or otherwise modified.

The number of new synthetic drugs that have as their central basis a benzene-ring structure linked to an NH_2 (amino) group, NH or N is legion, and before any one of them is used it might be wise for the

*My recent experience with myleran indicates that it may well replace both x-ray therapy and urethane in the treatment of chronic granulocytic leukemia.

physician to have a glance at the formula. For example, the antiepileptic drugs (Dilantin, Mesantoin and the like), the antihistamines, dexedrine and even the antibiotic chloramphenicol have one or more of these groupings, which in one way or another seem to be toxic to the bone marrow. What is toxic to the marrow may also be leukemogenic.

It can be seen that in the field of leukemia there is almost unlimited opportunity for investigation and, ultimately, advance. There is the added knowledge that what is found useful in the control of leukemia may turn out to be of value in the broader field of cancer control. Indeed, the leukemic states, with their many neoplastic cells floating free in the blood, offer a readily available subject for intensive study. The eventual control of leukemia, although perhaps not close at hand, is a real portent for the not too distant future.

References

1. Dameshek, W., Bloom, M. L., Weisfuse, L., Freedman, M. H., and Layrisse, M. *Chemotherapy of Leukemia and Leukosarcoma.* 54 pp. New York: Grune & Stratton, 1950.
2. Condensation of first two reports of Committee for Classification of Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs. *Blood* **4**:89-96, 1949.
3. Sacks, M. S., and Seeman, I. Statistical study of mortality from leukemia. *Blood* **2**:1-14, 1947.
4. Gauld, W. R., Innes, J., and Robson, H. N. Survey of 647 cases of leukaemia, 1938-51. *Brit. M. J.* **1**:585-589, 1953.
5. Best, W. R., and Limarzi, L. R. Age, sex, race, and hematologic classification of 916 leukemia cases. *J. Lab. & Clin. Med.* **40**:778, 1952.
6. March, H. C. Leukemia in radiologists. *Radiology* **43**:275-278, 1944.
7. *Idem.* Leukemia in radiologists in 20-year period. *Am. J. M. Sc.* **220**:282-285, 1950.
8. Ulrich, H. Incidence of leukemia in radiologists. *New Eng. J. Med.* **234**:45, 1946.
9. Amano, S. Radiation injury and leukemia in Japanese: cases observed in Hiroshima. Presented at a meeting of the International Congress of Haematology, Mar del Plata, Argentina, September 21-26, 1952.
10. Folley, J. H., Borges, W., and Yamawaki, T. Incidence of leukemia in survivors of atomic bomb in Hiroshima and Nagasaki, Japan. *Am. J. Med.* **13**:311-321, 1952.
11. Van Allen, W. W. Hazards of shoe-fitting fluoroscopes. *Pub. Health Rep.* **66**:375-378, 1951.
12. Dameshek, W. Physiopathology and course of polycythemia vera as related to therapy. *J. A. M. A.* **142**:790-797, 1950.
13. Stroebel, C. F., Hall, B. E., and Pease, G. L. Evaluation of radiophosphorus therapy in primary polycythemia. *J. A. M. A.* **146**: 1301-1307, 1951.
14. Selling, L. Preliminary report of some cases of purpura haemorrhagica due to benzol poisoning. *Bull. Johns Hopkins Hosp.* **21**:33-37, 1910.
15. Lignac, G. O. E. Die Benzolleukämie bei Menschen und weissen Mäusen. *Krankheitsforschung* **9**:403-453, 1932.
16. Mallory, T. B., Gall, E. A., and Brickley, W. J. Chronic exposure to benzene (benzol). III. Pathologic results. *Indust. Hyg. & Toxicol.* **21**:355-393, 1939.
17. Moeschlin, S. *Klinik und Therapie der Vergiftungen.* 430 pp. Stuttgart: Thieme, 1952.
18. Law, L. W. Induction of leukemia in mice following percutaneous application of 9,10-dimethyl-1,2-benzanthracene. *Cancer Res.* **1**:564-571, 1941.
19. Shay, H., Gruenstein, M., Harris, C., and Glazer, L. Transfer of myelogenous leukemia induced by gastric instillation of methylcholanthrene in Wistar rats. *Blood* **7**:613-622, 1952.
20. Ellermann, V. *The Leucosis of Fowls and Leucemia Problems.* 108 pp. London: Glydendal, 1921.
21. Johnson, E. P. Fowl leukosis: manifestations, transmission, and etiologic relationship of various forms. *Virginia Agr. Exper. Sta. Tech. Bull.* No. 76, 1941.
22. Gross, L. Mouse leukemia. *Ann. New York Acad. Sc.* **54**:1184-1196, 1952.
23. *Idem.* Biological properties of mouse leukemia agent. *Cancer* **6**: 153-158, 1953.
24. Bittner, J. J. Causes and control of mammary cancer in mice. *Harvey Lectures* **42**:221-246, 1946-1947.
25. Gross, L. Filterable agent, recovered from Ak leukemic extracts, causing salivary gland carcinomas in C3H mice. *Proc. Soc. Exper. Biol. & Med.* **83**:414-421, 1953.
26. Rosenthal, M. C., et al. Use of adrenocorticotropic hormone and cortisone in treatment of leukemia and leukosarcoma. *Blood* **6**: 804-823, 1951.
27. Wiseman, B. K., Doan, C. A., and Erf, L. A. Fundamental reciprocal relationship between myeloid and lymphoid tissues: its recognition, nature and importance as revealed by experimental and clinical studies. *J. A. M. A.* **106**:609-615, 1936.
28. Miller, F. R., and Turner, D. L. Action of specific stimulators on hematopoietic system. *Am. J. M. Sc.* **206**:146-158, 1943.
29. *Idem.* Relationship of myelokentric acid to steroid hormones. *Cancer Res.* (in press).
30. De Asua, J. T. Leukemias as diseases of adaptation (leukemia as general adaptation syndrome). *Rev. Soc. argent. hematotrap. y hemato.* **2**:269-301, 1950.
31. Videback, A. *Heredity in Human Leukemia and Its Relation to Cancer.* 280 pp. London: Lewis & Co., 1947.
32. Bierman, H. R., Byron, R. L., Jr., Kelly, K. H., and Cordes, F. Behavior of leukemic cells during continuous cross-transfusions between patients with leukemia and other neoplastic diseases. *Cancer Res.* **11**:236, 1951.
33. Goodman, L. S., et al. Nitrogen mustard therapy: use of methyl-*bis* (β-chloroethyl) amine hydrochloride and *tris* (β-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. *J. A. M. A.* **132**:126-132, 1946.
34. Dameshek, W., Weisfuse, L., and Stein, T. Nitrogen mustard therapy in Hodgkin's disease: analysis of fifty consecutive cases. *Blood* **4**:338-378, 1949.
35. Proceedings of Second Conference on Folic Acid Antagonists in Treatment of Leukemia. *Blood* Supp. **7**:97-190, 1952.
36. Dameshek, W., Freedman, M. H., and Steinberg, L. Folic acid antagonists in treatment of acute and subacute leukemia. *Blood* **5**:898-915, 1950.
37. Blood Research Laboratory, New England Center Hospital. Unpublished data.
38. Rhoads, C. P., Karnofsky, D. A., Burchenal, J. H., and Craver, L. F. Triethylene melamine in treatment of Hodgkin's disease and allied neoplasms. *Tr. A. Am. Physicians* **63**:136-146, 1950.
39. Silverberg, J. H., and Dameshek, W. Use of triethylene melamine in treatment of leukemia and leukosarcoma. *J. A. M. A.* **148**:1015-1021, 1952.
40. Haddow, A., and Timmis, G. M. Myleran in chronic myeloid leukemia: chemical constitution and biological action. *Lancet* **1**:207, 1953.
41. Galton, D. A. G. Myleran in chronic myeloid leukemia: results of treatment. *Lancet* **1**:208-213, 1953.
42. Burchenal, J. H., et al. Clinical evaluation of new antimetabolite, 6-mercaptopurine, in treatment of leukemia and allied diseases. *Blood* **7**:965-999, 1953.

CONTRIBUTIONS OF THE VIRUS LABORATORY TO COMMUNITY HEALTH*

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PHILADELPHIA

THE choice of this subject was made for two reasons: with the widespread control of bacterial diseases that has now been achieved, there is an increased recognition of the importance of viral and other nonbacterial diseases in the community; and it seems valuable at intervals to review the part that physicians play in the control of the health of the community of which their individual patients are integral parts. With these two points in mind, one may consider how a virus diagnostic laboratory works and enumerate the individual responsibilities of the physician using the laboratory and of the laboratory itself.

It is the experience of all physicians in general practice to be faced with a series of epidemics that travel through the community: one of the well recognized exanthems such as measles, infectious hepatitis or whooping cough. These are fairly easy to recognize from their clinical appearance alone. However, there are many others such as "grippe," epidemic nausea and vomiting, or diarrhea, for which an etiology can seldom be found. For aid in the accurate diagnosis of individual patients, physicians are accustomed to turn for help to the clinical laboratory and are acquainted with the appropriate procedures for the submission of specimens and interpretation of reports. I believe that they must now begin to accustom themselves to seeking the aid of the virus diagnostic laboratory in trying to obtain a more accurate diagnosis of the true etiology of these as yet undiagnosed community illnesses. This sharp distinction between individual and community health is made because, as pointed out below, the correct diagnosis of a viral disease in a patient may not be available until he has recovered from, or more rarely succumbed to, his disease. However, an accurate diagnosis in that particular case will alert the physician to the diagnosis of similar clinical situations that are present in the community so that he can apply any prophylactic or therapeutic agents that are available. Of course, clinicians are well aware that several different agents can produce a similar clinical picture,— for instance, interstitial pneumonia or meningoencephalitis,—but prophylaxis and even treatment may depend on recognition of the actual agent. Since one must therefore turn increasingly for help to the virus diagnostic laboratory, some of the ways in which the laboratory operates merit discussion. There are several different general technics, which can be listed as follows: isolation of agent; serologic tests; histologic examination; and electronmicroscopy (which is only mentioned here for completeness).

Isolation of the Agent

It is probably important to point out that taking of a specimen for viral isolation may necessitate adopting special precautions so that it is advisable, when possible, to discuss the details beforehand with the laboratory. For this reason, among others, this method of diagnosis is of less general practical value than the serologic method described below. Nevertheless, it has a place in certain circumstances — certainly, in the early determination of the etiologic agent in an epidemic. When influenza is suspected, for example, it is of the utmost importance to isolate the exact type or strain of influenza present for two reasons: to know whether the strain is one that is antigenically related to the strains incorporated into the available vaccines, and so that information may be recorded by the influenza center of the W.H.O. This center has been set up for making available, on a world-wide basis, information concerning any strains isolated so that new vaccines can be made, if necessary, ahead of the epidemic wave. A diagnosis can be made very quickly under suitable conditions. Throat washings are inoculated into the amniotic sac of embryonated eggs, which are incubated for forty-eight to seventy-two hours. The presence of influenza virus is made manifest by the agglutination of chicken or human red blood cells when these are added to the amniotic fluid. The strain can be identified by the demonstration that a certain type-specific antiserum inhibits this agglutination reaction. Isolation of the agent may be advisable in the epidemics of vesicular pharyngitis that frequently occur during the summer. To know that the Coxsackie Group A virus, which causes herpangina, is abroad in the community will alert one to examine the throats of young children with unexplained high fevers very carefully to spot the single vesicle that may be the only pathognomonic clinical evidence of the disease.

Apart from its value in epidemics, isolation of the virus as a method of differential diagnosis in some of the vesicular diseases of the skin and mucous membranes is a practical procedure. It is easy to obtain vesicle fluid, which can be dropped onto the chorioallantoic membrane of the egg. Within forty-eight to seventy-two hours quite characteristic pocks are caused by the viruses of variola, vaccinia, herpes simplex and cowpox. The two clinical conditions most commonly confused are perhaps vaccinia and herpes, when they occur in unusual sites (such as the vulva). The pocks on the egg membranes are strik-

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ingly different. Those of vaccinia are large and round, with necrotic centers and a mesodermal halo, whereas those of simplex are small, oval and without a halo. Smallpox and chicken pox form the classic diagnostic trap, and a correct differential diagnosis may obviously be of extreme importance. Variola produces very small pocks, something like herpes simplex, and these must be differentiated by other means, and varicella produces no pocks, being unable to grow on the membrane. The differentiation of herpes simplex, which occasionally occurs in a distribution following a nerve, and herpes zoster can be made in the same way; simplex produces pocks, and zoster does not.

The introduction of tissue culture by Dr. Enders and his group in Boston has opened up the possibilities of a much wider range of diagnostic tests. For instance, one of the major needs is an adequate routine method for the diagnosis of poliomyelitis. By the use of the tissue-culture method it is possible to isolate and type poliomyelitis virus from the stool in a suspected case within about forty-eight hours, although four to seven days is more usual.

It must be pointed out that in all these isolation procedures the final diagnosis depends on identification of the agent so isolated by means of a specific serum. Thus, a serologic test forms the backbone of almost all viral diagnostic work.

Serologic Diagnosis

This is the most important practical method of diagnosis, and comprises about 80 per cent of the work of a virus diagnostic laboratory. Of the technics used, the complement-fixation test is by far the commonest. For the purposes of this discussion the test is regarded as representative of all diagnostic tests of this sort.

If a patient's blood has no antibodies against a particular agent — for example, influenza A virus — at the beginning of a grippe-like illness but they appear in the blood taken at the end of the illness, the grippe-like illness will have been due to influenza A virus and not to any of the other organisms that might cause a similar picture.

It is to be noted that the diagnosis rests on the demonstration of a rise in the amount or the appearance of antibody during an illness, and this brings me to an important point in this discussion. If the laboratory is to be helpful to the clinician, the clinician must be of help to the laboratory. Successful diagnosis demands the closest possible teamwork, and it is well to consider just what each part of the team must do. It will be clear from the previous discussion that two specimens of blood are usually required for diagnosis — one taken very early in the disease. This is the difficult one to get, and I suggest that in the presence of a diagnostic problem in which a viral or rickettsial disease may be entertained in the differential diagnosis, a specimen of blood be taken when the patient is first seen. The hospital laboratory can separate it, and the serum can be sent to the virus diagnostic laboratory for immediate test in some cases or for storage. Then, later, if such an etiology is still in the running, a second specimen can be taken ten to fourteen days after the onset and sent to the laboratory, where both serums will be tested. The physician's first responsibility, then, is to obtain two specimens of blood. With the specimens it is essential that he also send some indication of his idea of the illness from which the patient is suffering. A good clinical description or the suggestion that a pneumotropic or neurotropic virus is suspected, or that a definite agent such as influenza or mumps is probably causing the symptoms, should accompany the specimens.

The laboratory in its turn must choose the appropriate antigens to use in the test. One reason why the laboratory can be much more helpful today than in the past is the fact that a number of antigens are becoming available commercially, in the same way as typhoid antigen is commercially available for the Widal test performed by the routine clinical laboratory. When presented with a pair of serums from a patient with a respiratory disease, for instance, the laboratory should use all the available antigens that might be of etiologic significance. The value of this procedure is illustrated by the following experience in Philadelphia. In the early part of 1948, a man was hospitalized with an illness that was puzzling but was finally diagnosed as influenza. Two serums were sent for confirmation of this clinical diagnosis. On test, however, the man was found to have been suffering not from influenza but from Q fever. Further investigation led to the discovery that an epidemic of Q fever had occurred in a wool-processing factory, an industry heretofore unsuspected of being associated with an industrial hazard of this sort, in a city not previously known to have encountered this agent at all.[1] Although the epidemic was diagnosed only in retrospect, it is obvious that the correct diagnosis could have alerted those in charge at the factory so that other cases would have been recognized clinically and appropriate antibiotic therapy used. This would have cut down the loss of man days, which averaged 14 per illness in this particular epidemic.

One of the more trying situations facing the physician is a patient with meningeal irritation in whom the cerebrospinal fluid may be under increased pressure and shows a mononuclear pleocytosis of moderate degree, normal sugar and chloride and possibly a slightly increased protein. The whole range of encephalitides appears at once in the differential diagnosis, as does poliomyelitis. The possibility of tuberculous meningitis or brain tumor also crosses the diagnostic horizon. It is here that the laboratory may be of immediate help in making a positive diagnosis of mumps meningoencephalitis. Since mumps, in my experience, is the most frequent of the diagnosable meningoencephalitides on the

eastern seaboard and may be unaccompanied by any evidence of parotitis in over 50 per cent of cases,[2] its presence should always be suspected in such a situation. The mumps virus has been found to have two antigens, soluble and viral. Antibodies against the soluble antigen of the mumps virus may appear as early as the second day after the onset of symptoms and may, therefore, be detected by suitable complement-fixation test in the first serum. Confirmation can be obtained by the demonstration of a rise in titer against viral and soluble antigens by comparison with the immediate and the convalescent serums in the usual way. When the pattern of antibodies against the soluble and viral antigens is examined, it is often possible to learn when the patient was infected with mumps. Early in the disease there is a high titer of antibody against the soluble, with a low or absent titer against the viral antigen. In convalescence there is a high titer of antibodies against both antigens. If infection has occurred more than two years previously, there is no antibody against the soluble but a low titer against the viral antigen. The practical value of this last piece of information is that it can be applied to relieve the anxiety of the busy man of affairs whose child is down with mumps. The chances that such a person, if he is a city dweller, has had mumps in the past, even without a history, is great, and can be proved by the demonstration that his blood has antibodies against the virus antigen. Such a test can also be useful for sorting out susceptible persons in a hospital when mumps occurs on the ward.

In closing this discussion on serologic methods I stress again, however, that the only way to provide a definite diagnosis is to demonstrate the rise of antibodies in the convalescent serum, since the mere presence of antibodies in one serum may only mean a previous forgotten or subclinical infection.

Histologic Examination

In superficial virus infections of the skin or mucous membranes an added tool is available. Punch biopsy can provide a relatively simple method of obtaining specimens for histologic study. A characteristic histologic picture of a given vesicular lesion can easily distinguish, for instance, smallpox and chicken pox or generalized herpes simplex. The lesions of simplex and chicken pox are identical, the vesicle is single and there is no necrosis of the corium, whereas in smallpox the vesicle is multiloculate and the corium is necrotic. The characteristic inclusion body in the latter is cytoplasmic, whereas in the former two it is intranuclear. In a case recently reported,[4] a seventy-eight-year-old man in Oklahoma developed a sudden generalized vesicular eruption, which was diagnosed as smallpox on the grounds that contents of the vesicles produced small plaques on the chorioallantoic membrane. A biopsy here could have helped clarify the situation. An extension of the histologic approach is the technic of examining a smear taken from the base of the lesion. In herpes simplex and the varicella-zoster group of infections characteristic virus multinucleate giant cells can be seen. Such giant cells do not occur in smallpox or other vesicular eruptions of the skin that might be clinically confusing.[5]

Discussion

After this brief review of how a virus diagnostic laboratory works and of some of the necessary interrelations between it and the practicing clinician, I should like to conclude by describing briefly the experience of the service rendered by a state health department virus diagnostic reference laboratory. In Philadelphia specimens and requests for advice are received from all over Pennsylvania and neighboring states. The annual report for 1952 showed that specimens were submitted from 1582 patients. From these 1582, such adequate follow-up specimens were received that tests could be completed on 1226, or 77 per cent, showing a high degree of clinician laboratory integration; 15,005 tests were performed before a conclusion was reached on these patients. In a review of the annual summaries for the last three years no epidemics of encephalitis were encountered, and hence no cases due to any of the arthropod-borne agents, such as the equine or St. Louis encephalitis viruses, were seen. Mumps and lymphocytic choriomeningitis together contributed 11 to 18 per cent of the total number of cases of encephalitis a year. Actually, this figure is higher and may be as much as 30 per cent, if one excludes patients whose meningeal signs were later found to be due to tuberculous meningitis or a noninfectious process. Among about the same number of cases diagnosed each year 6 to 9 cases of lymphocytic choriomeningitis and about three or four times as many cases of mumps meningoencephalitis have been found, with as many as ten times in a year with a high rate of cases of mumps. Of the 38 cases of mumps encephalitis diagnosed in 1952, 10 were submitted as possible cases of poliomyelitis. Among the meningoencephalitides investigated during this three-year period that were thought to be of viral origin but could not be diagnosed as such, 4 to 7 cases a year have been found to be toxoplasmosis, for a total of 16, and a total of 3 cases of leptospirosis, 2 of which were submitted as abortive poliomyelitis. I am sure that with improved diagnostic technics more of this last group will be discovered, and they must always enter into the differential diagnosis. Naturally, the epidemic incidence of various diseases will influence the relative frequency of differential diagnoses, as demonstrated by the large number of cases of mumps diagnosed among the neurologic patients in 1950, and the large number of cases of influenza among the patients with respiratory disease in 1951. It is also of interest

that there has been a fourfold increase in the incidence of psittacosis in the year that followed the lifting of the ban on the interstate transport of psittacine birds in 1952.

Summary

With the development and simplification of diagnostic methods the virus laboratory has come to occupy a definite niche in the over-all plans for maintaining community health at its highest level. It may be expected that this niche will grow as these methods are further improved and increasing use is made of this type of diagnostic facility by clinicians.

References

1. Sigel, M. M., Scott, T. F. M., Henle, W., and Janton, O. H. Q fever in wool and hair processing plant. *Am. J. Pub. Health* **40**: 524-532, 1950.
2. Kravis, L. P., Sigel, M. M., and Henle, G. Mumps meningoencephalitis with special reference to use of complement-fixation test in diagnosis. *Pediatrics* **8**:204-214, 1951.
3. Henle, G., Harris, S., and Henle, W. Reactivity of various human sera with mumps complement fixation antigens. *J. Exper. Med.* **88**: 133-147, 1948.
4. *Communicable Disease Summary for Week Ended April 18, 1953*. 4 pp. Washington, D. C.: Department of Health, Education and Welfare. Public Health Service National Office of Vital Statistics.
5. Blank, H., Burgoon, C. F., Baldridge, G. D., McCarthy, P. L., and Urbach, F. Cytologic smears in diagnosis of herpes simplex, herpes zoster and varicella. *J. A. M. A.* **146**:1410-1412, 1951.

ESOPHAGOAORTAL HIATUS HERNIA*

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THE literature is replete with excellent accounts of the clinical aspects and the surgical management of all of the classic types of diaphragmatic hernia. With the excellent contributions of Harrington, Sweet, Allison and others available, it is not the purpose of this paper to restudy this entire subject. We wish to review only briefly our cases of diaphragmatic hernia of all types as a background for the description of a special type of diaphragmatic hernia. During the past five years we have come to recognize a new and distinct type, which we prefer to designate as esophagoaortal hiatus hernias.

Table 1 presents our total experience of operative cases for the past ten years. Of the 140 cases less than half were done transabdominally and chiefly during the first half of this period. During the past five years repair has been done almost exclusively transthoracically. The largest group — that is, 61 cases — in which we were primarily interested in this study consisted of hiatus hernias repaired transthoracically.

Table 1. *Classification of Hernias.*

Type	No. of Cases
Esophageal hiatus hernia:	
Abdominal repair	49
Transthoracic repair	61
Space of Morgagni*	13
Traumatic*	10
Space of Bochdalek*	4
Eventrations*	3
Total	140

*Transthoracic repair.

In Tables 2 and 3 the pertinent clinical facts from the histories of these 61 patients with hiatus hernias are analyzed. Table 2 shows the age distribution, the greater incidence being in the middle and later decades of life. Table 3 demonstrates the incidence of symptoms in these patients; it is evident that actual pain or distress was the primary symptom leading to repair, although a large percentage of these patients also had definite complications that actually precipitated the admission for surgery. There were 46 patients, or 75.4 per cent, with this complaint. Regurgitation and vomiting, frequently self-induced, were manifested in 25 patients, or 41 per cent, and anemia was also noted in 25 patients, or 41 per cent. This symptom could not be proved in each case to be the result of the hernia. However, 11 patients, or 18 per cent, presented definite evidence of hemorrhage attributable to the hernia, which was relieved after the repair. The incidence of

Table 2. *Age Distribution.*

Decade	No. of Cases
30-39	6
40-49	16
50-59	25
60-69	13
70-80	1

Table 3. *Symptomatology.*

Symptom	Frequency of Occurrence %
Pain described as such or distress referred to as pain	75.4
Regurgitation or vomiting or both	41.0
Belching or flatulence or both	72.0
Dysphagia	18.0
Constipation	24.6
Overt manifestation of hemorrhage	18.0
Anemia	41.0
Obesity	54.0
Cardiorespiratory	13.0

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cardiorespiratory symptoms was 13 per cent, and it is with these symptoms that this study is primarily concerned.

If one is aware of the large number of patients with hernias who are treated successfully by conservative means — that is, weight reduction, diet and so forth — and of the many with this condition who are seen in a busy gastrointestinal department but who are asymptomatic and, furthermore, if the operative treatment is limited to the numbers mentioned above, it becomes evident that the surgical treatment of esophageal hiatus hernia is actually reserved for cases in which certain complications have arisen. It has not been our policy to advise surgical correction of small, asymptomatic hiatus hernias discovered on routine study or for the smaller hernias associated with mild symptoms that can be controlled by a medical and dietary regimen. However, operation has definitely been advised for the larger hernias in which the greater portion of the stomach or multiple viscera are involved or conservative treatment has failed to relieve the patient. In addition such complications as ulceration, hemorrhage, incarceration and obstruction are considered definite indications for operation. This is quite parallel to our present management of patients with duodenal ulcer, in whom failure of medical management or complications are the indications for surgical treatment.

Few difficult diagnostic problems are involved in this group of patients. Fluoroscopic and roentgenographic examination of the upper gastrointestinal tract, with special positional studies, is usually diagnostic. In a few cases in which ulceration is suspected or obstruction is present, esophagoscopy must be performed to rule out carcinoma in either the distal end of the esophagus or the cardia of the stomach involved in the hernia. We have found it essential to carry out a complete gastrointestinal roentgenologic examination, including gall-bladder study, to determine as accurately as possible whether the symptoms are primarily due to the hiatus hernia or to some other disease of the gastrointestinal tract such as cholelithiasis, cholecystitis or irritable colon. In this study 23 per cent of the patients with hiatus hernias had associated gall-bladder disease.

TABLE 4. *Follow-up Results of Transthoracic Repair of 61 Patients.*

RESULT	NO. OF CASES	PERCENTAGE
Follow-up data obtained	59	96.7
Followed 6 mo. or longer	51	83.6
Relief of symptoms	44	86.3*
Partial relief or mild recurrence	7	13.7*
Recurrence	5	8.2
With symptoms	3	5.0
Without symptoms	2	3.2

*Of 51 patients.

A follow-up examination or communication with the patients six months or longer after operation was made in 59 of the 61 patients, or 96.7 per cent (Table 4). Fifty-one, or 83.6 per cent, were followed for six months or longer with complete relief of symptoms in 44, or 86.3 per cent, of this group. Five of these patients, or 8.2 per cent, reported a small recurrence of their hernia; 2 of these, however, were asymptomatic.

With this brief presentation of the general symptomatology, indications for operation and operative results, it is interesting to study more carefully some of the symptoms produced by hiatus hernia and particularly their relation to an anatomic subclassification of this type of hernia. The symptoms of hiatus hernia are varied and complex because of the structures involved. They depend on the amount of mechanical interference with the function of the herniated abdominal viscera, the degree of interference with the normal function of the diaphragm and the amount of increase in pressure that the herniated viscera produce within the thorax and mediastinum, causing impairment of respiration and circulation. Distention and pressure on and stretching of the viscera in addition to the bowel apparently lead to various reflex neurogenic phenomena. A number of patients manifested bizarre symptoms, such as fainting, psychomotor disturbances and peculiar radiation of pain. There was also the group in which a cardiac origin of the pain and symptoms

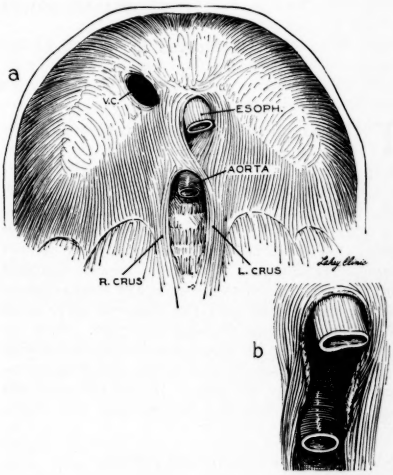


FIGURE 1. *Anatomy of the Diaphragm, Showing the Normal Relation of the Esophageal Hiatus and Aortal Hiatus with the Crura* (a) *and the Diaphragmatic Defect Present in Esophagoaortal Hiatus Hernia* (b).

was suspected long before the diagnosis of diaphragmatic hernia was made.

Over the years we have come to recognize a type of hernia that is a subclassification of the esophageal hiatus hernia but is associated with a much higher incidence of reflex cardiorespiratory symptoms. A significantly higher incidence of symptoms varying from an anginal type of pain to almost classic asthmatic attacks has been found in this group. This herniation through the diaphragm is through a defect extending anteroposteriorly from the esophageal hiatus to the aortal hiatus (Fig. 1*a* and *b*). This complete muscular defect between the two structures results in a herniation that extends originally through the esophageal hiatus into the mediastinum behind the heart. As it enlarges, it is limited above by the hilar structures and eventually expands into each half of the thorax, overlapping the cardiac shadow on either or both sides (Fig. 2). As already stated, this interesting type of hernia is associated with a particular symptomatology. In addition to the minimal gastrointestinal complaints commonly associated with hiatus hernia, the major presenting symptoms simulate those of respiratory-tract or cardiac origin. These symptoms are pain, angina-like in character and radiation, cough and wheezing simulating asthma. Although careful study of the cardiorespiratory systems is essential in the differential diagnosis these symptoms have been relieved only by adequate repair of this special type of diaphragmatic hernia.

In the following cases the patients presented symptoms referable to the cardiac and respiratory systems.

Case Reports

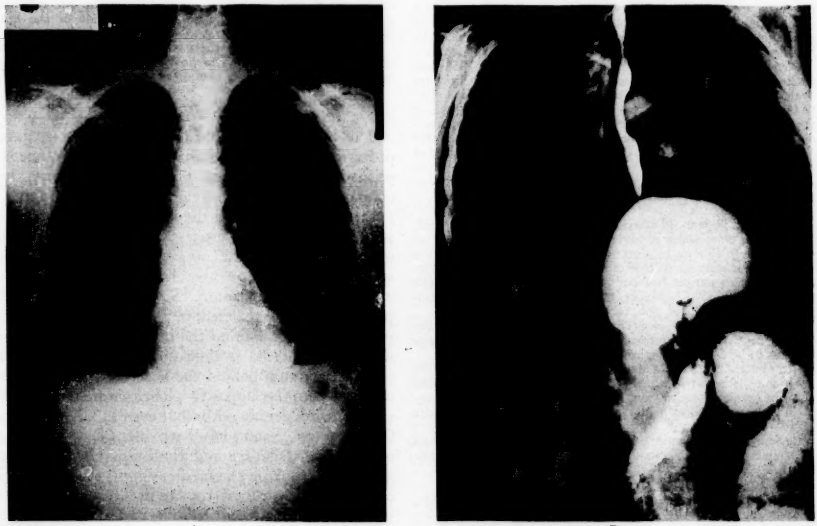
Case 1. A 43-year-old married woman was seen at the clinic on October 10, 1952, complaining of asthma and a cough of 18 months' duration. She had been treated on several occasions, both in and out of a hospital, with bronchodilators, antibiotics, expectorants and so forth and, finally, on one occasion with ACTH. The attacks frequently followed an upper respiratory infection and were manifested as a severe bronchospasm with retained secretion and infection. Skin tests showed no reaction to any of the common food and dust substances. The extraction of infected teeth was of no consequence. There was no family history of allergy. She was known to have a diaphragmatic hernia during the period of study and treatment.

Physical examination on admission revealed wheezing throughout both lung fields and coarse rales at both lung bases.

Laboratory studies were negative except for a sedimentation rate of 40 mm. per hour. Stereoscopic films of the chest demonstrated a large, cyst-like mass, with a fluid level in the posterior mediastinum, rising to a level of 9.5 cm. above the diaphragm and visualized on either side of the heart borders, with a transverse diameter of 12 cm. The presence of a hiatus hernia was confirmed by a barium meal.

On November 4 bronchoscopic and esophagoscopic examinations were performed. Normal mucous membrane was observed in the esophagus and hernia. A bronchogram revealed bronchospasm.

On November 7 a large esophagoaortic type of diaphragmatic hernia was reduced and repaired transthoracically.



A B

Figure 2. *Characteristic Film of the Chest* (A) *and Barium-Swallow Study* (B), *Demonstrating the Herniation into the Mediastinum behind the Heart.*

Since operation this patient has been well and relieved of her respiratory symptoms. On April 4, 1953, roentgenograms of the esophagus and stomach gave no evidence of recurrence of hernia.

CASE 2. A 48-year-old single woman was seen September 20, 1950, complaining of substernal pain of 3 years' duration that was frequently associated with weakness, perspiration and faintness. She was treated for "coronary thrombosis."

An electrocardiogram was normal. She was observed by us during an attack of definitely constrictive pain of fairly severe degree. Roentgenograms revealed a rounded mass behind the heart, with a fluid level representing a hiatus hernia.

At the time of operation on October 11 a large hernia was found that extended up the mediastinum to the level of the hilus of the lung. A large defect between the esophagus and aorta was repaired.

This patient has had no postoperative roentgenologic examination, but on May 23, 1953, she reported that she had had no further symptoms.

CASE 3. A 40-year-old married woman stated that she had not been well for 16 years. She complained of intermittent nausea and occasional vomiting. She had 1 severe episode of pain substernally and in the mid-dorsal region, for which she had been hospitalized. She was told she had "cardiac asthma."

Physical examination showed an obese woman. Pain was elicited when she attempted to flex her dorsal spine. Pressure over the lower sternum precipitated a severe episode of inability to breathe, with development of marked deep-purple cyanosis of the upper part of the chest, neck and face, which lasted approximately 2 minutes. An electrocardiogram was normal. A roentgenogram revealed an area of density behind the heart that contained a fluid level.

The diaphragmatic hernia was repaired on August 17, 1949. This patient reports that she is well except for "gas pains."

CASE 4. A 59-year-old married woman was seen July 17, 1950, complaining of episodes of severe pain under the left breast of approximately 18 months' duration that usually began while she was eating; one severe episode of substernal pain was relieved by vomiting. This patient had been told that her attacks were due to "heart trouble." She had been treated with morphine. Nitroglycerin failed to relieve symptoms.

Roentgenograms revealed cholelithiasis and an area of decreased density in the retrocardiac area of the chest that was thought to be due to a diaphragmatic hernia.

After weight reduction a cholecystectomy was done on May 19, 1951, and the hernia was repaired transthoracically on November 28. The hernia extended from the normal position of the esophageal hiatus to the aorta, with complete separation of all muscular fibers.

Barium-swallow examination on September 9, 1952, showed no recurrence of the hernia, and the patient was asymptomatic when seen May 20, 1953.

CASE 5. A 64-year-old woman was seen on December 18, 1946, complaining of nocturnal orthopnea and severe substernal burning pain of 3 years' duration. She stated that she "had to jump out of the bed and go to an open window for air." This lasted an hour and was accompanied by wheezing.

Examination of the heart and lungs was negative. An electrocardiogram showed left-axis deviation. Roentgenologic and fluoroscopic examination disclosed an area of increased density overlying the right side of the heart.

A diaphragmatic hernia was repaired on April 30, 1947. The postoperative course was complicated by a bilateral pleural effusion and possible phlebothrombosis of the left leg. Anticoagulant therapy was given. She was also treated with digitalis during the postoperative period and after leaving the hospital.

When seen January 20, 1949, she did not have nocturnal dyspnea and had not taken digitalis for 6 months.

CASE 6. A 56-year-old married woman was initially seen at the clinic in 1941 complaining of excruciating pain in the retrosternal area, accompanied by pain in the left shoulder and usually occurring after a meal. Roentgenologic examination at that time showed the stomach to be completely inverted, with the greater curvature at the level of the base of the heart. She was treated conservatively for pain, nausea, vomiting and occasional dysphagia.

When seen in June, 1950, she complained of more severe substernal and shoulder pain and was studied for angina pectoris. An electrocardiogram was normal and barium-swallow examination again showed the stomach overlying the heart shadow and the mediastinum.

At operation on September 25, 1951, the hernia extending to the base of the heart was reduced, and a defect extending to the aortal hiatus and to the right of the esophagus was repaired.

There were no complaints referable to the hernia when she was seen at the clinic in September, 1952, and May, 1953.

CASE 7. A 73-year-old married woman was seen on May 8, 1952, complaining of cramping epigastric pain of 3 months' duration and of severe palpitation and weight loss of 3 years' duration. The palpitation had been relieved by digitalis.

An electrocardiogram was normal. Roentgenologic examination revealed a soft-tissue shadow in the inferior mediastinum that proved on examination after administration of barium to be a hernia. At operation on May 26 a large hernia was found that extended superiorly to a point just below the arch of the aorta. Complete relief was reported on follow-up study in May, 1953.

CASE 8. A 66-year-old married woman was seen at the clinic on March 18, 1953, complaining of constricting or "pressure-like" precordial pain simulating angina. Examination of the heart was normal, as was an electrocardiogram at the clinic.

A roentgenogram of the chest showed a larger hernia behind the heart shadow. A large esophagoaortic defect was repaired on March 20, with relief of symptoms.

DISCUSSION

The operative approach to this deeply situated posterior defect in the diaphragm is best accomplished with the patient in the lateral position, left side up. A posterolateral incision is made, the eighth rib being removed, and the ninth rib cut posteriorly near the transverse process. When the pleura is opened the herniation may or may not be readily visualized and frequently is completely obscured within the mediastinum. A simple crush of the phrenic nerve is carried out, and the mediastinal pleura is opened behind the inferior pulmonary ligament. The hernia is then dissected carefully from the mediastinum behind the heart, with precautions not to open the opposite pleura, which is usually adherent to deeply situated hernias of this type. Once the esophagus has been identified, the lower end of this structure and the hernial sac are freed and delivered from the mediastinum; the diaphragm can then be cleared of areolar tissue, and the defect identified. In this particular type the defect will be found extending posteriorly from the esophageal hiatus to the aortal hiatus with the right crus of the diaphragm lying medially and the left crus forming the lateral rim of the defect (Fig. 1*a* and *b*). Since these are sliding hernias it is not essential to remove the peritoneal sac, but it must be opened to ensure that the proximal end of the stomach is freed of all adhesions and that the stomach can be freely reduced into the abdomen and not compressed or "accordionated" immediately below the diaphragm, which will almost certainly lead to a recurrence.

The previous difficulty of maintaining reduction is no longer a problem with present anesthetic agents, including the muscle-relaxing drugs such as Anectine. The distal end of the esophagus is placed anteriorly in the hernial defect against the strong, firm decussation of the crura and tacked there by a few interrupted silk sutures to maintain it in its proper rela-

tion until the repair is completed. Starting at the posterior limit of the defect — that is, at the aorta — heavy interrupted silk sutures are placed through the clearly defined edges of the right and left crura and

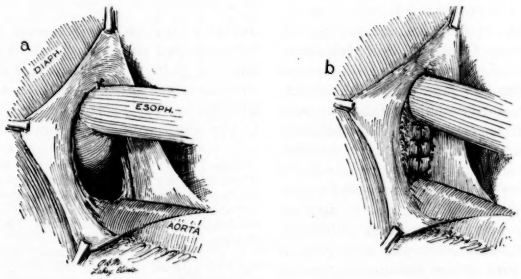


FIGURE 3. *Operative Management of Esophagoaortal Hernia, Showing the Diaphragmatic Defect as Visualized with the Hernia Reduced into the Abdomen* (a) *and the Crura Closed Anteroposteriorly between the Esophagus and the Aorta* (b) *with Repair of this Defect.*

the defect closed progressively anteriorly until the posterior edge of the esophagus is reached (Fig. 3*a* and *b*). The last stitch next to the esophagus should bring the diaphragm up snugly around this structure so that only the tip of the index finger can be introduced alongside it. The mediastinal pleura is then loosely closed, and the thorax closed, an intercostal catheter for suction being left to help rapid re-expansion of the lung. A Levin tube, which is introduced into the stomach preoperatively, is also kept on suction postoperatively for forty-eight hours. A carefully graduated intake is allowed after operation, and early ambulation is started. In the 8 cases in which this lesion has been definitely recognized and this type of repair carried out there has been complete relief of cardiorespiratory symptoms and whatever minimal gastrointestinal symptoms the patients had as well, and to date there has been no evidence of recurrence of the hernias repaired in this manner.

SUMMARY AND CONCLUSIONS

An interesting subtype of hiatus hernia is described. The defect in the diaphragm is primarily of esophageal hiatus origin, but with progression of the hernia in size, the right and left crura are separated anteroposterior to the aortal hiatus. As a result, a sliding hernia develops into the mediastinum behind the heart, giving rise to a significantly higher incidence of cardiorespiratory symptoms, which vary from the typical anginal type of pain to almost classic asthmatic attacks. Relief of these symptoms has been obtained by the type of repair described.

THROMBOSIS OF THE DEEP LEG VEINS DUE TO PROLONGED SITTING

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"SPONTANEOUS" thrombosis, according to DeCamp, Landry, Ochsner and DeBakey,[1] represents between 4 and 5 per cent of all venous thrombosis in the limbs (the lower limbs almost exclusively). The very word indicates that the conditions under which the disease occurs in ambulatory persons have not been recognized. How sudden muscular efforts and strains may cause thrombosis in the deep lower-leg veins of even young and active men has been pointed out by Crane,[2] but such an influence is as often absent as present. Perhaps Naide's[3] account of thrombosis in tall men gives a better hint of the nature of the exciting factor. It suggests that prolonged dependency stasis, a state imposed by airplane flights, automobile trips and even attendance at the theater, is able, unpredictably, to bring on thrombosis of this sort. During the London "blitz" pulmonary embolism often followed immediately on long periods of sitting in air-raid shelters, as described by Simpson.[4] His account reveals the nature of the insecure propagating process in the deep veins of the calf, notably in how few hours of sitting still a fatal thromboembolism may be set up. As a preventive, he pleads for bunks in the shelters. The cases described below indicate the importance of recognizing the prolonged sitting position as the occasion of a not too rare disease.

CASE 1. An active 54-year-old physician flew from Boston to Venezuela on July 4, 1946. The flying time was about 14 hours, in hops of 6 or 7 hours. In Caracas he was much on his feet, and he returned on July 7. On this flight he took short naps, but his calves did not rest upon a support, though he crossed his knees at times. On reaching home, an hour or 2 after leaving the plane, he noticed lameness in his right calf, but hobbled about on that day (July 8).

On July 9, examination revealed slight deep tenderness over the posterior tibial vessels, rather high in the calf, and definite painful resistance to dorsiflexion of the foot. There was no edema, cyanosis or skin infection (such as might cause popliteal adenitis). A diagnosis of deep phlebothrombosis was made. The prothrombin was found to be 100 per cent.

Having easy access to a blood laboratory and with active teaching to do, the patient desired to remain ambulatory. A semielastic bandage was worn from toes to knee, to maintain as far as possible an even venous compression, and he was given 300 mg. of Dicumarol. During the 2 succeeding days, smaller doses followed, and on July 12, the 3d morning after the disease had been noticed and treatment started, pain and lameness, already lessened on the previous day, were found to be absent. The prothrombin was 15 per cent, and there was slight oozing of blood from the nose. From this time on, no medication was used. Complete recovery followed and has since been maintained.

Immediately after a long airplane flight, a well localized venous thrombosis, in one of the major vascular systems of the upper calf, accompanied by a mild inflammatory reaction, was favorably influenced by Dicumarol and gave no further signs as soon as the prothrombin fell to 15 per cent. Evidently a very early process was checked and healed before it had time to spread. The rapid disappearance of pain and lameness was remarkable, but since the treatment of such an early, acute disease, without bed rest, is so rare an event, it is impossible to say whether or not it should have been expected.

CASE 2. A 53-year-old business man, accustomed to long hours of sitting at his desk, had suffered 8 months earlier a partially obstructing thrombosis of his left femoral artery, presumably of arteriosclerotic origin, which had nearly obliterated all arterial pulsations at and below the knee. There were no other local changes.

In January, 1952, without known cause, he awoke one morning with a tense, lame, left calf. On the following day, his left ankle and foot were found to be cyanotic and slightly edematous. The posterior calf muscles strongly resisted dorsiflexion. A small pulmonary embolism was suspected but not proved.

Treatment by elevation in bed, exercise, bandaging and Dicumarol for 10 days restored the leg to its previous state, except for slight irritability of the posterior muscles.

On May 4, 1953, the patient flew from Guatemala to New York by way of Cuba and Miami, in hops of about 2 hours, with exercise at stops and without sleep. Four days after his return he awoke with a sore, lame, swollen left leg, but was not seen for 3 days, after which he was hospitalized and treated with Dicumarol as before. There was a satisfactory recovery. Two months later his leg had returned to its previous state.

This patient is obviously thrombophilic. Only his second and most severe attack of thrombosis followed his airplane flight. The disease has remained confined to the deep vessels of the lower left leg.

The following cases of deep lower-leg phlebothrombosis followed long automobile trips.

CASE 3. A 19-year-old college girl, on April 13, 1939, immediately after a drive by automobile from Nebraska to Boston, complained of lameness in her left calf, which rapidly became tense and tender to the touch, especially on its inner upper posterior face. She was confined to bed, and moist heat was applied. There was no fever.

When first examined, 4 days later, the leg was still enlarged, but was soft and only slightly tender to deep palpation just below the popliteal space. There was typical slight resistance and discomfort on forced dorsiflexion of the foot, with cyanosis on dependency. No enlarged or thrombosed superficial veins were observed.

Treatment for 10 days by confinement to bed, the foot of which was elevated 10 cm., without restriction of motion, was followed by apparent recovery, but 4 weeks later, there was a sudden return of all complaints. In a phlebogram (by way of the lesser saphenous vein at the ankle) the deep calf veins could not be visualized, the popliteal and femoral vessels being incompletely filled.

Because a recurrence of a deep lower-leg venous thrombosis seemed to have occurred, the femoral vein was interrupted just distal to the profunda and a good current of blood was found. Some femoral adenitis was noted.

Six months later, the left leg appeared normal, showing only slight cyanosis of the great toe on dependency.

Evidently this patient's constitutional background was abnormal, for three years later she suffered a high femoral thrombophlebitis of the right leg (successfully treated by lumbar sympathetic block)

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and since that time has given signs of lupus erythematosus which, in 1949, had not proved fatal.

CASE 4. A somewhat obese 56-year-old man of sedentary habit, took a vacation in September, 1940, in the form of an automobile tour. Early in the trip, he noticed an unaccountable lameness in the right calf, which after a few days lessened, but he found it difficult to secure a comfortable position for his leg. On September 22 he noticed cough and, 4 days later, pain in the left anterior portion of the chest increased by respiratory movement. For the next 2 months he continued to have varying amounts of cough and dyspnea, with occasional attacks of faintness. Finally, hemoptysis led to an x-ray examination, which revealed a pulmonary infarct. The earlier lameness of the right leg was then remembered, and the thromboembolic picture was put together.

On November 7 examination of the right leg showed slight tenderness, without swelling, below the bulge of the right calf, with discomfort and resistance on forced dorsiflexion of the foot. There was some cyanosis on dependency. Moist rales in the right side of the back and dullness over the lower left lobe were observed. A diagnosis of phlebothrombosis in the right lower leg, with recurrent pulmonary embolism, was made.

At operation on November 7 exploration and interruption of the right superficial femoral vein demonstrated a free flow of blood in the femoral vein without thrombosis at this level. A good recovery was followed by normal health except for a slight tendency to swelling of the right ankle.

The connection between the unaccustomed long automobile ride and the phlebothrombosis is evident. The case is much like that in one of Naide's[3] tall men who developed a deep venous thrombosis during a 3000-mile automobile ride. The patient was fortunate not to have died of pulmonary embolism and in being cured by a femoral-vein interruption.

CASE 5.* A 59-year-old man sat for about 2 hours at the theater with his legs crossed, walking about at one intermission. On walking home he felt an ache in the right calf and on undressing thought the lower leg slightly discolored. On the following morning tenderness on lateral compression of the upper right calf muscles and discomfort on forced dorsiflexion of the foot were found. He had suffered no injury or strain.

Treatment at home with Dicumarol, elevation, bandaging and exercise in bed was followed by recovery and subsequent normal health.

This case is much like those reported in the air-raid shelters.[4] Which leg was crossed over the other at the theater was not recorded.

*I am indebted to Dr. John Homans, Jr., for permission to include this case.

DISCUSSION

As is so often true of venous thrombosis, this group of cases reveals a tendency rather than a proved relation of cause and effect. Considered in connection with thromboembolism of the London air-raid shelters, it suggests that the prolonged sitting position occasions a degree of dependency stasis that may result in the rapid development of a quiet type of thrombosis in the deep veins of the calf. From this, a propagation of clot and pulmonary embolism may immediately follow. It is probable that thrombosis is more prompt to occur when one or both of the legs rest on some sort of support, causing the kind of injury to the venous endothelium demonstrated by O'Neill's[5] experiments in Dr. Cecil Drinker's laboratory. The rhythmic forward, pulsatile motion of the foot, often noticed when one knee is crossed over the other, shows that the popliteal artery of the crossed leg is likely to be compressed in this position and warns that it may be a cause of venous stasis as well. Such matters are important enough to suggest the advisability of making movements of the toes, feet and lower legs when one is sitting for long periods and of getting up and exercising when opportunity offers. The right leg seems more susceptible than the left. There is evidence that persons over fifty years of age should have this particularly in mind and that physicians should be alert to recognize the significance of lameness after airplane flights, automobile trips and other occasions of a prolonged seated position. The administration of anticoagulants, combined with bed rest, elevation and elastic bandaging of the legs, should be curative.

REFERENCES

1. DeCamp, P. T., Landry, R. M., Ochsner, A., and DeBakey, M. E. Spontaneous thrombophlebitis. *Surgery* **31**:43-54, 1952.
2. Crane, C. Deep venous thrombosis in leg following effort strain. *New Eng. J. Med.* **246**:529-533, 1952.
3. Naide, M. Spontaneous venous thrombosis in legs of tall men. *J. A. M. A.* **148**:1202, 1952.
4. Simpson, K. Shelter deaths from pulmonary embolism. *Lancet* **2**: 744, 1940.
5. O'Neill, J. F. Effects on venous endothelium of alterations in blood flow through vessels in vein walls, and possible relation to thrombosis. *Ann. Surg.* **126**:270-288, 1947.

SPECIAL ARTICLE

THE PHYSICIAN'S INCOME TAX*

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NEW YORK CITY

TO maintain his "books of account" properly, so that they will be available for income-tax purposes, a professional man should be aware which items are those of income and which are those of expense. The following discussion deals with income and expense arising only from professional activities.

PROFESSIONAL INCOME

All payments received from patients whether in the form of cash or check are treated as income at the time of receipt. If a patient's check is returned by the bank because of "lack of funds" the amount is dropped from income until it is paid. If the sum is never paid it does not become a "bad debt" for tax purposes since under the cash basis of keeping books such a sum is never treated as an item of income; this applies equally to charge patients who do not pay their bills.

Ordinarily, gifts received from patients, such as those made during the Christmas season, may not be includable in income, but if a patient, out of gratitude, pays more than he was billed, the additional payment is an item of income since it is connected with the services rendered.

When fees are paid by patients in the form of services or goods, either for office or for personal use, the fair market value of the services or goods received is treated as an item of income.

REFERRAL INCOME AND EXPENSE

The acceptance or payment of referral fees is a violation of the rules of ethics prescribed by local and national medical societies; moreover, definite tax consequences may result from such transactions. In all cases referral income is taxable as ordinary professional income to the practitioner. The United States Supreme Court has recently ruled that the payment for the referral may or may not be deductible as a business expense, depending on whether it is contrary to "sharply defined national or state policies the frustration of which may, as a matter of law, preclude the deductibility of an expense" of this type. Even when specific state legislation forbids payment of referral fees, and this practice exists, the referrer must include the receipt of the fee in income; however, the referee may not deduct such a payment as an item of expense.

PROFESSIONAL EXPENSE

Substantial tax savings may be accomplished by proper records of expense and awareness of what items may be treated as expense items, since such items are reflected in the income-tax return as deductions from gross income.

As an illustration, an unmarried practitioner who reports $12,300 taxable income (after expenses and personal exemption of $600) pays a tax of $3,940 based on 1953 tax rates. Failing to deduct $300 of deductible business expense increases the tax by $144 since the tax on $12,000 is $3,796.

Another advantage of keeping close track of items of expense is that in years in which income is high, if one's records are up to date, outstanding bills may be paid before the end of the year to minimize the tax impact on such high income. Conversely, expense may be high in a given year and income low, and so it may pay to let the outstanding bills run into the following year, when income may be higher.

Professional expense is expense in connection with the conduct of a practice that is "ordinary and necessary." An expense need not be a recurring item to be "ordinary"; it suffices that the item be one that is common in conducting the practice. If the expense is appropriate and aids in the conduct of such practice it is treated as "necessary."

The following discussion of particular items of expense parallels "Schedule C" of the Federal Income Tax Return on which professional expense is entered under "Other Business Deductions."

Salaries and Wages

The total amount paid during the taxable year to a nurse, office assistant or other professional employee is a deductible business expense. Included in this amount is the weekly withholding made on the employee's salary. Contributions made as an employer to Social Security are not reported here.

Wages paid to a child or another member of a taxpayer's family are deductible, provided the services were actually performed and were related to the conduct of the practice.

If payments are made to an employee other than by cash, the fair market value of the property given may also be deducted. Bonuses or Christmas presents given to employees are a salary expense since they originate out of the employment.

Payments to a cleaning woman or other domestic may be deducted here, provided the services were performed in connection with office practice. If the office is located in the home and the domestic performs work in both the office and home, an alloca-

*Adapted from the chapter on "Accounting Practices" in the forthcoming book, *The Physician, His Practice and His Business*, by permission of the publishers, Little, Brown and Company, Boston.

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tion of the payment, based on the amount of time devoted to cleaning of the office, must be made.

Office Rent

When the office is not located in the home the amount deducted is the amount of rent paid to the landlord each year. Brokerage expense incurred in obtaining a lease or legal fees in connection therewith must be allocated over the life of the lease.

When the office is located in the home and the physician is a tenant and not the owner of the premises the rental must be allocated so that the rental attributable to the running of the office may be determined. The allocation may be based on the relative rental value of the part used for home or office or on the ratio of space for such purposes.

Any items of the landlord's expense one is required to pay, such as taxes on the property, are treated as rent expense. Any repairs made to the premises may also be deducted, and if they apply to both home and office an allocation must be made. Capital improvements made to rented premises, such as erection of partition walls for an office, must be depreciated over the life of the lease or the life of the improvement, whichever is the shorter period.

Interest Expense

Interest expense incurred in the conduct of a practice is fully deductible. Such an expense may arise from the purchase of equipment "on time" or from a bank loan made to equip the office.

When the office is located in the home and interest is paid on a mortgage, an allocation of the expense, based on the ratio of office space to personal space, should be made. The balance of the interest may be taken as an interest deduction on page 3 of the income-tax return.

Business Tax Expense

During the course of the year many taxes are paid, of which some are wholly related to business, some mixed, and some wholly personal.

Taxes that relate solely to the profession, such as annual license fees, narcotic fees, sales tax on medical equipment and social-security contributions made as an employer, are deductible in full.

Mixed taxes, such as a real property tax where the office is located in the home, must be allocated. The percentage allocated to office use is deducted in Schedule "C"; the balance may be deducted on page 3 of the tax return under "Taxes." Gasoline taxes, when the car is used for both business and pleasure, receive the same treatment.

Excise taxes as a rule are not deductible unless they are connected with business purposes. Therefore, only the percentage of telephone and telegraph taxes attributable to the practice may be deducted. The balance of such a tax may not be deducted on page 3. The same treatment is accorded to a tax on a railroad ticket.

Occupation taxes, such as local taxes on gross receipts from the practice, are deductible in full.

Depreciation and Obsolescence

Property used in the practice that has a useful life of more than one year becomes subject to a depreciation or obsolescence allowance.

Depreciation is a gradual process that extends over a period of years during which capital assets, such as an x-ray machine, sterilizer, office furniture, technical books, medical equipment and car, wear out. Obsolescence occurs when a piece of equipment becomes obsolete because of technical advances or legislation banning its use and therefore has no further value. In either event a deduction is permitted to be taken on the tax return, and a shorter useful life is accepted when one is determining the allowance to be taken for obsolescence.

Useful life of a particular piece of equipment must be ascertained before a depreciation schedule is made up. The Treasury Department has stated that as a general rule the useful life of "professional libraries is 30 years, while the life of scientific equipment used by dentists, doctors, etc. is usually 10 years." Factors that may lessen the period of useful life are excessive use, climatic conditions or purchase of second-hand equipment.

When equipment is known because of one's experience to have a useful life of less than ten years, the manufacturer should be requested to note that fact on the bill. When second-hand equipment is purchased, the length of time it has been used should be ascertained and its condition on purchase noted, so that the remainder of its useful life can be determined.

To the extent that professional equipment may have salvage value, such a value should be subtracted from its cost before a depreciation deduction is made. Thus, if a new x-ray unit costs $1750 and its salvage value after ten years is estimated to be $150, the annual depreciation deduction taken will be $160 — that is, $1750 − $150 = $\frac{\$1600}{10}$.

With reference to depreciation of buildings (when the office is located in the home or used solely for the practice) the factors used are location and physical condition of the structure. Ordinarily, when a building is of good construction and properly maintained its useful life if it is built of brick is fifty years, and if it is of frame construction, forty years. Only the part of the depreciation allowable to business use may be deducted, when the office is located in the home.

In determining the amount of depreciation to be taken on an automobile, one may assume a useful life of four to five years, depending on the type of practice in which it is employed, conditions of roads in the area, weather conditions and the type of car. When the car is used for both business and

pleasure, an allocation of depreciation must be made, and only the part attributable to business use may be deducted. It is advisable to maintain and preserve mileage records for an average week, so that the amount of such mileage used for both purposes may be calculated, to justify the allocation to be made.

Situations will arise during a practice in which one will be considering replacement of old equipment or an automobile. Normally, this may be done by way of trade-in, the old equipment in addition to cash being turned over to the dealer. Sometimes, the old equipment may be sold to a second-hand dealer for cash, and new equipment purchased from another dealer. There are important tax considerations that may determine which method will be more profitable, and if one is considering such a disposal an accountant or attorney should be first consulted.

Repairs

Another deductible item taken on the tax return is the cost of repairs during the year. Repairs are usually made to keep property in good working order, and are to be distinguished from improvements, which prolong the life of the property. An improvement is the subject of a depreciation allowance to be taken over the useful life of the improvement; a repair is deductible in full in the year paid.

Items that may be deducted are painting of the outside and inside of a building, and plumbing and electric repairs. Items to be treated as improvements are installation of new roofs and replacement of heating apparatus, old cooking equipment or an old sink or an air conditioner.

It should be noted that in either event, when the office is located in the home, an allocation must be made to determine the amount attributable to the business needs.

Other Business Expense

There are many items of expense that do not fall into special categories, and are lumped into a miscellaneous grouping identified as "other business expense." Among these items are the following:

Professional dues. This includes dues paid to local and national medical societies as well as any excise tax charged on such dues. Should one join local groups such as Kiwanis or a Chamber of Commerce for business reasons, membership dues may be deducted.

Technical journals and magazines. The full cost of technical journals and newspapers and magazines for the waiting room may be deducted. However, technical books have a useful life longer than a year, and must be depreciated.

Legal and accounting fees. Fees paid to an attorney or accountant for services relating to the practice are deductible in full. It should be noted that the charge for such services that do not relate to production of income may not be deducted. If an attorney or accountant has performed work of business and personal nature, the charge for each type of service should be itemized on the bill.

Insurance expense. The cost of insurance premiums relating to professional coverage may be deducted. Other items such as life-insurance premiums that relate to personal expense may not be deducted.

Items of professional insurance expense are those relating to automobile, fire, liability, malpractice, theft, radium, forgery, fidelity and accounts-receivable premiums. When the same policy covers business and personal needs, an allocation of the premium cost must be made. Allocation must also be made when a lump sum is paid for three-year coverage; only the amount attributable to a particular year may be deducted in that year.

Medical and office supplies. The cost of supplies used in one's practice may be deducted in full. Since a physician is engaged in selling services rather than supplies, he need not maintain an inventory of unused supplies. He should make certain that these items are paid by check and that paid bills are preserved to justify the deduction of the cost of such items.

Entertainment expense. A reasonable amount of the cost of entertainment expense connected with one's practice may be deducted. Such an expense must be "ordinary and necessary," as noted above, and must have some connection with the practice rather than incurred in the "hope" that professional income will result therefrom.

Accurate records for this type of expense, including the names of the guests, must be maintained, since recent announcements by the Treasury Department indicate that entertainment expense will be scrutinized very carefully in the future.

Telephone and telegraph expense. The cost of the monthly telephone bill attributable to one's practice, including the excise tax, is deductible in full. A record for a "test day" should be run to determine the amount of this charge attributable to personal and business use. The monthly charge for a telephone-answering service is also deductible.

Traveling expense. The cost of trips away from home to attend medical conventions is deductible in full. This includes such items as railroad fare, lodging, meals and incidental expense, such as tips. The cost attributable to a member of the family accompanying one on such trips may not be deducted. A detailed record of the expenses incurred, such as cost of railroad fares and hotel bill, should be kept. Entertainment expense incurred during such trips must be connected with the profession.

Utility expense. The full cost of heat, light and gas may be deducted, so far as such items relate to business use.

Charitable contributions. Contributions that are made to charitable organizations for professional

reasons may be deducted in full, without the normal 20 per cent limitation of adjusted gross income. A contribution made to a medical group of a local community-chest drive would be treated as a business charitable contribution. Whereas one may not deduct the value of the time devoted to free clinics, and so forth, the cost of gasoline and similar supplies used in going to and from the clinic may be deducted.

Postgraduate education. One may not deduct the cost of acquiring a medical education at college or medical school, nor may one deduct the expense of taking "board" examinations. In addition the cost of postgraduate courses to prepare one for a specialty may not be deducted.

Recently, however, it was held that the expense incurred by a specialist in attending a course relating to his specialty could be deducted, since such attendance had a direct relation to the production of professional income by the specialist, and the expense was attributable to his need to keep abreast of new procedures.

Uniforms and laundry expense. The cost of office uniforms may be deducted, as well as the laundry charges and repairs. One may also deduct these costs for linens and towels. If a rental service is employed, the full rental cost may be deducted.

The following check list of professional expense will enable one to keep track of deductible items:

Accountants' fees relating to the practice.
Attorneys' fees relating to the practice.
Automobile expense, including maintenance, chauffeur's salary, insurance, depreciation, garage, rent, parking fees, tolls, license fees and plates.
Board and lodging furnished an employee for the employer's convenience.
Books, magazines, newspapers, flowers, cigarettes for the waiting room.
Christmas presents or bonuses to employees.
Cleaning woman's wages.
Charitable contributions.
Depreciation of office equipment, building, books.
Electricity expense.
Entertainment expense.
Gifts to hospital attendants and nurses.
Interest attributable to office.
Insurance premiums.
Medical and office supplies.
Professional dues.
Repairs to equipment and office.
Rent, including any other charges one may have to pay.
Salaries paid to nurse, assistant and domestics.
Taxes, including those on sales, license fees, real property and gross receipts.
Telephone and telegraph expense.
Travel expense.
Uniform and laundry expense.

MEDICAL PROGRESS

NEUROLOGY

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WE have attempted to select for discussion, from the many papers bearing on neurologic problems that have appeared since our last review, studies increasing understanding of the normal function of the nervous system or making clearer the nature of the biochemical derangement in certain neurologic disorders, as well as others that describe new procedures of value in diagnosis and therapy of neurologic diseases.

PHYSIOLOGY

Cerebral Cortex

Additional criticism of the notion of a rigid point-to-point representation of muscles or movement in the cortex has been advanced by Walshe.[1] His criticism is supported by the observation of Liddell and Phillips,[2] who, in testing motor responses to electric stimulation of the cortex of young baboons, observed large overlap of areas in the cortex from which contralateral movements could be elicited when single pulses of 1 to 5 milliamp. and 5 milliseconds in duration were employed as stimuli. Stimulation of these overlapping areas at about 25 cycles per second provoked a spread of movement from fingers to wrist and more proximal joints. With further increase in frequency of stimulation, this simple pattern of representation was found to dissolve into the classic motor map.

Woolsey and his collaborators,[3] using the range of stimulus frequency found by Liddell and Phillips[2] to yield the classic patterns of representation of movement in the cortex, observed arrangements of motor representation in cortex of monkeys that are interrelated in much the same manner as the actual

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musculature of the body. Observations made by these investigators bring into question the long-accepted picture of a complete separation of face and trunk areas by interposition of the arm area. They found that fingers and toes and lower face are represented within and near the contralateral central sulcus. Representation of the axes of the limbs was found to run rostrocaudally through the contralateral motor area in such a manner that the proximal parts of the limbs are better represented rostrally; the upper face is also rostrally and contralaterally represented. The representational axis of the leg was found to be medially located to that of the arm. Face, arm and leg representations were observed to be all bound together by an area for the trunk musculature, which forms the rostral border of the entire motor area as outlined by Woolsey et al.[3] This rostral border was considered to correspond approximately to the rostral limit of the Vogts area 6a alpha and to the most rostral limit of the Hines strip area. At the lateral edge of the entire field, an ipsilateral motor-face area was demonstrable. Woolsey and his co-workers state that the total area defined by their stimulation studies does not coincide with any single cytoarchitectonic field, and, hence, they consider it best to call this region the "precentral motor area." In addition to this precentral motor area, Woolsey's group found evidence for a second complete representation of the contralateral somatic musculature on the medial wall and on the dorsal bank of the sulcus cinguli, rostral and ventral to the precentral motor area. This second area corresponds to the human supplementary motor area of Penfield and Rasmussen.[4]

Representation of movement in regions of cortex outside the classic precentral motor area is reported by Penfield and Rasmussen,[4] who state that in their stimulation of human cortex, approximately 20 per cent of motor responses elicited from cortex adjacent to the central fissure were obtainable from the postcentral area. Responses from postcentral gyrus were produced after removal of the adjacent portion of the precentral gyrus, indicating that these responses do not depend on collateral connection with the precentral gyrus or on physical spread of the stimulating current.

Experiments of Sloan and Jasper[5] and Marshall and his co-workers[6, 7] have cast serious doubt on the existence of specific suppressor strip areas in the cortex. These authors have suggested that the suppression of spontaneous electric activity and reduction of somatomotor activities, which have been produced by stimulation of these areas, are actually due to the elicitation of the spreading depression, which was described by Leão and Morison[8] and which is nonspecific in the sense that it can be evoked from any area of the cortex. Marshall has expressed doubt that spreading cortical depression is a normal physiologic phenomenon; he considers it an interesting but abnormal reaction that has confused experiments on cortical excitability since the time of Fritsch and Hitzig. He has shown that the phenomenon can readily be obtained by deterioration of the experimental preparation as the result of cooling of the cortex and radical internal dehydration.

Temporal Lobe and Its Connections

Many years ago Hughlings Jackson described the psychic symptoms (amnesia, panic state, confusion) that may occur in convulsive seizures. He pointed out that the motor part of such seizures is rarely convulsive, and usually consists of the performance of automatic acts during the period of amnesia or confusion. He called these psychic episodes automatisms and ascribed them in some cases to lesions of the temporal lobe. The term psychomotor seizure has been used more recently to designate this type of seizure. Penfield and Kristiansen[9] explored surgically 20 patients with automatisms and found that 17 had lesions in the temporal lobe or sylvian region, 2 in the frontal lobe, and 1 in the inferior parietal lobule. Features of the psychomotor attacks were produced by electric stimulation of the brain in 16 patients. Nineteen out of a total of 25 responses were elicited from the area including the anterior temporoinsular cortex and the region of the claustro-amygdaloid complex and the anterior hippocampus.[10]

Gibbs[11] has stated that abnormal spike potentials arising from the temporal lobe are found in 30 per cent of patients with this type of epilepsy when the tracings are made in the waking state and in 90 per cent when the patients are asleep. Jasper and Penfield[12] also state that the foci as determined by electrocorticography are predominantly in the region of the tip of the temporal lobe. They have found, however, that only about half their patients with temporal-lobe foci demonstrable by electroencephalography had seizures that could be called true automatisms. They have also made it clear that psychomotor attacks are only one type of focal cortical seizure arising from the temporal lobe and that not all psychomotor attacks are necessarily of temporal cortical origin, some seeming to be subcortical and others arising from the frontal lobes.[13-16]

Penfield[17] reported on the effects of surgical excision of abnormal brain tissue in the treatment of psychomotor seizures. Ninety patients were explored, all but 3 of whom were found to have visible atrophic lesions. The attacks were arrested in 51 per cent of the surgically treated patients followed for one to ten years.

Reticular Formation

The function of the reticular formation in the brain stem has been elucidated through recent experimental work of Magoun.[18] The reticular formation of the brain stem appears to be a rostral enlargement and specialization of interneuron collections that are present throughout the intermediate gray column of the spinal cord. Both bear the same

topographic relation to the central canal, and are interposed between afferent and efferent elements. Ascending and descending intraspinal connections between spinal interneurons, subserving intersegmental activity within the cord, are examples, Magoun has stated, of comparable connections of reticular formation in the brain stem. This work[18] has demonstrated that, by means of its descending connections, the reticular formation of the brain stem is capable of modifying activity within the spinal cord, either reducing or augmenting it. On the other hand, the cephalic influences of the central reticular formation on the cerebral hemispheres seem to provide the substrate of the waking state on which most higher functions of the nervous system depend.

Magoun has shown that when motor activity is initiated in an anesthetized decerebrated animal and stimulation is applied to the bulbar part of the reticular formation, the movement previously induced is brought completely to a halt. This suppressor action has a broad influence on the spinal reflexes, being effective on the two neuron-arc tendon reflexes, on multineuronal flexor reflexes and on cortical motor responses that are known to involve interneuronal transmission through the dorsal part of the spinal gray matter. This descending suppressor pathway from the bulbar reticular formation is distributed in the anterolateral white matter of the cord. Its influence is most pronounced on the ipsilateral side, but crossed effects are also present, the crossing occurring at spinal rather than at bulbar levels.

In contrast, when backgrounds of spinal motor activity are induced and intercurrent stimulation is delivered to the reticular formation at levels of the brain stem above the bulb, an opposite effect to the suppressor influence of the bulbar reticular substance is observed, facilitation of movement ensuing. The facilitatory reticular spinal system takes origin from levels of the brain stem as far forward as the diencephalon, excellent effects being elicited from stimulation of the midline and intralaminar nuclei of the thalamus and from its nucleus ventralis lateralis. The subthalamus and hypothalamus are likewise exceedingly effective regions for facilitation. Excitable foci may be followed caudalward from those more rostral structures through the periaqueductal gray, the midbrain and pontile tegmentum, and the bulbar reticular formation. At the bulbar level, facilitation is evoked from stimulation around the periphery of the suppressor field, and rebound facilitation after bulbar suppression suggests that the two systems are partially coextensive here.

Experiments involving stimulation and destruction of the rostral portion of the central reticular substance and the midbrain and diencephalon have revealed the importance of reticular substance in the maintenance of the waking state. This is the portion of the reticular formation that exerts pronounced facilitatory influences on spinal-cord activity, and Magoun[18] points out the possibility that it normally functions in both ascending and descending directions and thus subserves, on the one hand, "behavioral facility, and on the other, the central alertness, which characterizes the waking state."

Ward and his associates[19, 20] have shown in a series of experiments that stimulation of the reticular substance in the monkey produces the alternating tremor characteristic of paralysis agitans and that destruction of certain areas of the reticular substance is followed by the appearance of this tremor.

ACTH and Cortisone

When the many impressive claims began to appear concerning the diverse therapeutic effects of ACTH and cortisone, it was hoped that these agents would have curative or ameliorative influences on some of the neurologic disturbances, especially the degenerative disorders, for which there is no satisfactory treatment. Considerable information is now available concerning the action of these hormones on a variety of diseases of the nervous system. Merritt[21] has reviewed the experience at the Neurological Institute, and has compared his findings with those obtained in other clinics. He lists the following neurologic disorders in which ACTH and cortisone have been employed: progressive muscular dystrophy, myotonia atrophica, myotonia congenita, myasthenia gravis, amyotrophic lateral sclerosis, peripheral neuritis (including the Guillain–Barré syndrome), multiple sclerosis, epilepsy, acute anterior poliomyelitis, chorea, postvaccinal encephalitis, progressive lenticular degeneration and paralysis agitans. Also to be included in this list are Bell's palsy[22] and dermatomyositis.[23]

Twenty cases of progressive muscular dystrophy treated with ACTH or cortisone have been reported. In 9 cases of the juvenile or facioscapulohumeral type there was no appreciable effect on the strength of the patient or on the course of the disease. In contrast with the poor results in the juvenile form, Shy and McEachern[24] described excellent results in the treatment of patients with the type of muscular disorder that they call "menopausal dystrophy," because of the relatively late onset of the symptoms; good to excellent results were reported in 7 of 8 patients with this type of muscular dystrophy. Merritt[21] treated 3 cases of muscular dystrophy in women in whom the onset of symptoms was in middle life, but found no significant change in muscular status of the patients.

Fifteen cases of myotonia atrophica have been treated. Negative results were reported by Milhorat[25] and Glaser and Merritt.[26] Moderate or great improvement in myotonic symptoms was reported by Shy and McEachern[24] in 3 cases and by Reese and Peters[27] in 7 patients; however, no significant improvement in the muscular strength of any of these 10 patients was seen. Shy and McEachern[24] de-

scribed complete abolition of myotonia in a patient with myotonia congenita treated with ACTH. The myotonia was greatly decreased, but not abolished, when cortisone was administered by mouth.

Reports have appeared on 36 patients with myasthenia gravis treated with ACTH or cortisone.[21] In a small percentage of cases administration of these compounds is not accompanied by any significant change in the clinical condition of the patient. In the majority, however, there is a temporary exacerbation of the symptoms during the period of therapy, followed by a remission of symptoms in a slight, moderate or great degree. The remission is rarely complete, consisting mainly of a decrease in the daily prostigmine requirement, and is often followed by a relapse. Repeated treatment is usually followed by another remission.

Thirteen patients with amyotrophic lateral sclerosis have been treated with these agents. No appreciable benefit was noted in these cases or in 8 patients with multiple peripheral neuritides treated by Merritt[21] and Shy and McEachern.[24] Stillmann and Ganong[28] and Seltzer et al.[29] reported improvement in muscular strength and apparent shortening of the clinical course in patients with polyneuritis of the type classified as Guillain–Barré syndrome.

Glaser and Merritt[26] treated 33 patients with multiple sclerosis. Twelve showed changes suggestive of significant improvement. In most cases improvement was transient, appearing only during the course of treatment and lasting only a week or two after its discontinuation. A small series of cases was kept on maintenance doses of ACTH or cortisone in an attempt to determine whether long-term administration of these compounds will prevent acute relapse of the disease. Merritt[21] concludes that although transient improvement may be noted in individual symptoms it can hardly be claimed that the treatment of this disease with these compounds is on the whole satisfactory. A number of cases of multiple sclerosis have been treated by Thorn et al.,[30] with results similar to those reported by Glaser and Merritt. Eighteen patients with acute retrobulbar neuritis occurring as a symptom in the course of multiple sclerosis or as an isolated phenomenon have been treated.[21] Improvement in visual acuity and decrease of size of scotomas and lessening of pain, decrease of the edema of the optic nerve and increase in visual acuity, one to ten days after initiation of treatment, have been reported. This series of cases with retrobulbar neuritis is too small to permit one to draw any conclusions, and the reported results are not significantly different from those obtained without therapy or with other forms of treatment in this disorder.

In 3 patients with epilepsy treated by Glaser and Merritt[26] there was no change in the frequency of seizures. Electroencephalographic activity became more abnormal in 1 patient. Klein and Livingston[31] described improvement in the seizure incidence and the electroencephalograms of 4 of 6 children with epilepsy. Russell et al.[32] reported that there was improvement in the epileptiform seizures associated with lupus erythematosus under ACTH treatment although 1 of their patients had convulsions for the first time coincidental with the administration of the hormone.

Neither cortisone nor ACTH has any beneficial effect on acute anterior poliomyelitis or infectious mononucleosis with cerebral involvement, amaurotic familial idiocy, progressive lenticular degeneration or paralysis agitans. Glaser and Merritt[26] and Aronson, Douglas and Lewis[33] treated 3 cases of chorea without benefit. Schwarz,[34] however, reported improvement in 2 patients with a severe form of the disease. Cortisone has also been described as having been helpful in treatment of a patient with Bell's palsy.[22]

Vascular System

Cerebral Angiography

Injection of radio-opaque material into a carotid artery to outline the cerebral blood vessels radiographically for diagnostic purposes was introduced by Egas Moniz of Lisbon over twenty-five years ago.[35] This technic was utilized in Europe with considerable enthusiasm soon after its introduction, but has been employed widely in the United States only in recent years. Four monographs[36-39] give detailed consideration to cerebral angiography, and of especial interest is that of Lima,[36] since it reports on the experience gained with this procedure in over two thousand examinations done in the Lisbon clinics of Egas Moniz.

Under the conditions routinely employed by many clinicians, injection of one carotid artery results usually in the filling of the anterior and middle cerebral arteries on the side of the injection; in only about a fourth of the examinations done in the Lisbon clinics was the posterior cerebral artery on the injected side filled as well, and, rarely, the contrast medium made its way into the basilar system or into vessels on the side opposite the injection. Failure to fill the posterior cerebral artery is not a serious defect, because it is the least important of the three major cerebral arteries from the arteriographic standpoint, and because it is rarely displaced by tumors or the site of vascular lesions.[40] This limitation of angiography has been overcome by a radiographic device described by Curtis[41] that takes twenty exposures in ten seconds. Curtis states that its use attains filling of the posterior, as well as of the anterior and middle cerebral arteries, on the injected side in practically all cases after injection of radio-opaque material into the carotid artery.

Photography of the images on a fluorescent screen with a motion-picture camera gives promise of affording a more comprehensive understanding of the movement of the segment of blood labeled with contrast medium through the cerebral blood vessels.[39] Relations of the arterial, capillary and venous phases

of angiography may be well defined by this technic although radiographic contrast in the venous phase may not always be clear. Considerable technical improvement in this method of recording must be made before it is practicable for most hospitals. The usefulness of this procedure in avoidance of error in angiography is well illustrated in a passage from Hamby's[39] monograph:

> Recent review of a cineroentgenographic study of a case having a large subclinoid aneurysm was most instructive .... The lesion visualized early in the angiogram; the diodrast "puddled" in the sac of the aneurysm. One could see it fade progressively as successive pulsations of the vessel brought in fresh blood that gradually swept away the contrast material. The emerging blood stream never contained sufficient diodrast to allow it to be visualized beyond the aneurysm. Interval films made in such a case might very well have led to a diagnosis of thrombosis of the internal carotid artery above the aneurysm.

Angiography, of course, is of especial importance in diagnosis of vascular lesions and tumors of the brain. The indications for carotid angiography have been divided by Bull[40] into five main groups: subarachnoid hemorrhage (congenital and other aneurysms, bleeding angiomas and bleeding tumors); arterial occlusion; craniocerebral injuries (extradural, acute subdural and intracerebral hematomas); sequelae of trauma (chronic subdural hematomas, and arteriovenous fistula at cavernous sinus — a rare occurrence); nontraumatic, intracranial expanding lesions (certain aneurysms and angiomas that have not bled, neoplasms, abscesses and granulomas).

With pneumoencephalography, ventriculography and cerebral angiography available as aids in diagnosis of neurologic disorders, the clinician is frequently confronted with a difficult problem of selection of methods. With full recognition of the limitations of such a schematization, Bull[40] has suggested the following rules as a guide in choice of methods: if a vascular lesion of any kind is suspected, angiography is clearly indicated first; if a supratentorial tumor is diagnosed and confidently lateralized by clinical or plain radiologic methods, angiography is indicated first; if a lesion of the midbrain or posterior fossa is suspected, ventriculography is indicated first; and if a nonvascular or nontumor lesion, such as cerebral atrophy, is suspected, pneumoencephalography is indicated first.

A technic for percutaneous vertebral angiography has been described by Sugar et al.[42] that appears to be simple to use.[39] The limited value of vertebral angiography has been stressed by Bull,[40] who points out that it is a painful procedure under local anesthesia, since it is almost impossible to avoid striking sensory nerves in probing for the artery. Further, the petrous temporal bones cast heavy shadows in the lateral view and obscure the arteries of the posterior fossa. The arteries that are well filled in vertebral angiography — the basilar and the superior cerebellar — are mostly inaccessible to present surgical methods. Thus, aneurysms found on the course of these vessels cannot usually be treated. The relative unimportance angiographically of the posterior cerebral artery, also filled after vertebral injection, has already been pointed out. Bull also states that pneumoencephalography and positive contrast ventriculography are such accurate methods in the localization of lesions of the posterior fossa that it is difficult to imagine their being superseded by arteriography.

It is scarcely necessary to emphasize that even the diagnosis of aneurysms cannot always be made by angiography. Krayenbuhl[43] described 3 proved aneurysms that failed to fill on arteriography, and Alpers and Ryan[44] reported 2 cases of aneurysms of the internal carotid artery in which the diagnosis was made clinically but arteriograms failed to disclose the aneurysms found at surgical exploration. (It has been claimed[39] that the aneurysms can be visualized in the films of 1 of the cases discussed in the paper by Alpers and Ryan.[44])

An effort to ascertain the value of the angiogram in diagnosis of tumors has been made by investigators at Johns Hopkins University and the University of Illinois.[45] Several clinicians read a series of 200 angiograms performed on consecutive patients suspected of having brain tumor in whom the diagnosis was subsequently verified. The attempt at diagnosis was made by the examiners without knowledge of the clinical histories. Attention was given to three considerations: pathological diagnosis, location of tumor and adequacy of films for interpretation. A correct pathological diagnosis was made in 36 per cent of the cases (range for the examiners was from 23 per cent to 48 per cent). A correct localizing diagnosis was made in 73 per cent (range, 66 per cent to 77 per cent). In 10 per cent the films were considered inadequate, and in 17 per cent the lesion was either not seen or incorrectly localized. Principal errors in identification of the type of tumor occurred in calling a metastasis either a glioblastoma (when it had a vascular pattern rich in vessels) or an astrocytoma (when it was poor in vessels). Almost as many errors were made by mistaking an astrocytoma for a glioblastoma, or vice versa. Unless calcification occurred, oligodendrogliomas could not be identified at all. Rarer tumor types were invariably missed. Lesions that displaced major vessels were usually called astrocytomas, and these were found to be correctly diagnosed by this criterion in most cases.

Although the complications of angiography were not emphasized in the earlier literature, it has become increasingly clear that they are of sufficient frequency and severity to be important. In discussing the incidence of complications in their series of 108 patients, Dunsmore, Scoville and Whitcomb[46] report untoward reactions in 14, or approximately 10 per cent. In general, these complications appear to be due to the agent employed as a contrast medium. Whereas in Europe Thorotrast is most

frequently used, in this country Diodrast seems to be preferred. Dunsmore et al.[46] (who used Diodrast) reported 3 deaths, 4 cases of hemiplegia with permanent residual effects and 2 transitory hemiplegias. In addition 2 patients had convulsions, and 1 a thrombosis of the carotid artery; in 1 the cervical sympathetic chain was injured. The technical details of proficiency of injections, quantity of material injected and medication used in arteriography were not considered significant factors in the etiology of complications. The condition of the patient appeared to be of outstanding importance. Highest incidence of complications was found in older patients with "thrombotic tendencies," and in patients with evidence of impaired cerebral circulation. Dunsmore and his associates[46] call attention to the delayed nature of most of the serious complications and considered it probable that cerebral thrombosis secondary to irritative vasospasm is the etiologic basis of the complications. Poppen has also stressed the importance of vasospasm in production of the complications of angiography, and warns that angiograms should not be done under local anesthesia unless the superior cervical ganglions and carotid sinuses are thoroughly anesthetized with procaine before the contrast medium is introduced.[46]

Foltz, Thomas and Ward,[47] in a careful study of the physiologic effects of Diodrast on animals and human beings, found evidence for both a vasospastic and a cytotoxic action. Midway in the intracarotid injection, the pial vessels of monkeys under direct observation showed a fluttering effect, and toward the end of the injection a blanching of the pia was observed (vasoconstriction), lasting for sixty to ninety seconds and followed by pial blushing (vasodilatation), lasting usually for several minutes. These effects were seen more dramatically when cool rather than warm Diodrast solutions were used. A drop in intracranial pressure was associated with the vasospastic period, and an increase in intracranial pressure occurred during the vasodilatation stage. Complex electroencephalographic changes were also produced. Unilateral stellate-ganglion block reduced the vascular influences of Diodrast, but the cytotoxic effects were increased. The authors suggest that the vasospastic effect may be protective so far as the cytotoxic action of Diodrast is concerned and conclude that measures to counteract vasospasm are contraindicated. They also state that although major complications occur relatively infrequently, diffuse damage, including neuronal death, may occur with Diodrast angiography, and this hazard must be weighed against the information to be obtained by angiography in any particular patient.

Occlusion of Internal Carotid Artery

Cerebral angiography has made possible a clearer understanding of the syndrome of partial or complete occlusion of the internal carotid artery. The importance of this disorder was emphasized in 1899 by Gowers[48] and in 1914 by Hunt.[49] Egas Moniz and his collaborators,[50] in 1937, were the first to describe cases of this condition diagnosed by arteriography. Its frequency is indicated by an incidence of 1 per cent in all arteriograms performed in Egas Moniz's clinic. Thrombosis of the internal carotid artery can occur from the second decade to the seventh; the highest incidence appears to be in the fifth and sixth decades.[51] Etiologically, it is most often related to arteriosclerosis and occasionally to thromboangiitis obliterans.[51] The two commonest sites of thrombosis are near the point of origin of the internal carotid artery and in the intracranial portion of this vessel close to its termination at the circle of Willis.[51] Denny-Brown[52] has pointed out that this disorder should be considered in patients with recurrent neurologic symptoms apparently related to vascular disease of the brain. Numbness of the face or extremities, weakness or paralysis of the face, arm or leg and aphasia persisting for a short time and followed by improvement, perhaps with complete remission, are characteristic symptoms. Blindness may or may not occur. Arterial pulsations in the neck may appear to be full and normal on both sides. Denny-Brown[52] has suggested that many of the cases of transient neurologic symptoms attributed to spasm of cerebral vessels are due to insufficiency of the carotid or basilar artery. He has also called attention to the fact that recurrent symptoms referable to the nervous system can occur on the basis of partial occlusion of the basilar artery, especially in its lower third. Symptoms of basilar involvement include attacks of mental confusion, blindness or unconsciousness, with residual bulbar dysarthria.

Arteriography is the principal means of demonstrating thrombosis of the internal carotid artery. If cerebral vessels are viewed after the injection of the dye normal or increased circulation in the external carotid branches may be seen, and the branches of the internal carotid artery are invisible. Occasionally, the lumen of the part of the artery that lies within the sinus or beyond it is seen to be narrowed, irregular and abnormally straight, and flow through the anterior and middle cerebral arteries is decreased or blocked. Sometimes, the stump of the internal carotid artery, about 2 cm. or less in length, may be seen in the film of the neck when the occlusion occurs close to the common carotid artery. Denny-Brown has also urged caution in the use of arteriography in elderly patients, because of the danger of producing thrombosis in extremely atheromatous vessels. He has described two clinical tests that may be of value in diagnosis of this disturbance.[53] Observation of the fundus on the side of the suspected lesion while the opposite carotid artery is compressed or while light pressure on the globe of the eye is exerted with the finger discloses narrowing of retinal vessels, if they derive their circulation from the opposite carotid artery. He states that these tests are positive in only about

half the cases, probably because of the presence of external carotid collaterals, compression of the carotid artery on the side of the symptoms will also reproduce the symptoms in about half the cases. Denny-Brown[53] regards a history of repeated episodes of paralysis in the same limb as the most characteristic feature of the syndrome.

Etiologic Factors in Vascular Accidents

Wilson and his associates[54] in Philadelphia studied a series of 542 patients in whom evidence of an acute cerebrovascular accident was found at autopsy. The medical history, clinical examination or autopsy gave evidence of cardiocirculatory insufficiency in 83 per cent of these patients. These authors believe that their findings indicate that systemic circulatory inadequacy plays an important part in the causation of cerebrovascular accidents, and that preventive measures and therapy should be oriented toward maintaining and restoring general circulatory efficiency to as great a degree as possible. Their experience with stellate-ganglion block has not been as favorable as that of others, and they point out that a number of patients with cerebrovascular accidents show a gratifying degree of spontaneous recovery, and hence evaluation of results of therapy is difficult in this disorder. They remark that it is possible that some of the effects of stellate-ganglion block are the result of improvement of systemic circulatory efficiency, since improvement after block has been reported in paroxysmal atrial tachycardia and atrial fibrillation. They do not consider the condition of the general cardiocirculatory state to be the sole factor but rather one of the more important factors in the etiology of cerebrovascular disease.

Muscular Dystrophy

Since the demonstration by Levene and Kristeller,[55] in 1909, of an increased excretion of creatinine in patients with disorders of muscle many studies and speculations have appeared concerning its significance. Creatinuria, with an associated decrease in creatinine excretion, occurs in various functional disorders of musculature and in diseases associated with muscular wasting. It has been described in severe forms of myasthenia gravis, myotonia atrophica, amyotrophic lateral sclerosis, poliomyelitis (with atrophic muscles), dermatomyositis and generalized myositis fibrosa, as well as in endocrine disorders, and is especially prominent in the muscular dystrophies.[56] Recent studies in the normal and pathologic metabolism of creatine make the significance of creatinuria somewhat clearer.

Observations on animals[57] indicate that creatine is formed in a series of reactions beginning with transfer of an amidine group from arginine to glycine to form guanidoacetic acid (glycocyamine); subsequently, guanidoacetic acid is methylated by methionine to produce creatine. These reactions are found to occur mainly in liver and kidney. Creatine appears to be the unique precursor of creatinine, which is formed by removal of a water molecule from creatine, a process thought to occur predominantly in muscle. There appears to be considerable species variation in the capacity of liver and kidney to carry out the synthesis of creatine.[57] An attempt to identify the site of synthesis in man has recently been described, in which catheterization of the hepatic and renal veins of normal subjects was employed.[57] The concentrations of creatine, creatinine, guanidoacetic acid and arginine in blood removed from the hepatic and renal veins were compared with those in samples of arterial blood removed almost simultaneously. Calculations from these experiments were interpreted as indicating that the rise in creatine concentration across the liver is sufficient to account for the total known rate of daily creatine synthesis, and it was concluded that this organ is the major site of synthesis of creatine in the human being.

Isotopic technics have been employed by Roche et al.[58] in an experiment designed to test hypotheses concerning the biochemical defect in muscular dystrophy that leads to creatinuria. These investigators believed that the presence of creatine in urine might be explained either by an elevation of the blood level in excess of the renal threshold as a result of a leakage of creatine from diseased muscle or by a failure of the muscle mass to remove from the blood creatine formed at a normal rate by the liver. If the first hypothesis is true, urinary creatine and creatinine should have a similar isotopic concentration after the administration of a creatine precursor. If the second hypothesis is correct, immediately after the feeding of a precursor, urinary creatine should be isotopically richer than urinary creatinine. In support of the second hypothesis, it was found that after administration of N^{15}-labeled glycine, to a patient with muscular dystrophy, the initial concentration of N^{15} in creatine was approximately ten times that in creatinine. On the basis of these two reports, creatinuria seems to be the result of failure of diseased or reduced muscle mass to remove from the blood the creatine produced at a normal or nearly normal rate by the liver, with a resulting accumulation of creatine in the blood, which eventually exceeds renal threshold. It should be emphasized that this concept rests on observations in 6 normal male subjects, in the creatine-synthesis study, and on a single isotope experiment in the investigation of the mechanism of creatinuria, as well as on several experimental assumptions made in both investigations.

A number of cases of progressive ophthalmoplegia beginning in adult life have been found to include pathologic changes in the ocular muscles, suggesting a primary muscular disorder related to muscular dystrophy. Kiloh and Nevin[59] describe 5 such patients and suggest that many of those with ptosis and a slowly progressive paralysis of the ocular

muscles, formerly considered to have "chronic nuclear ophthalmoplegia," are actually suffering from a myopathy. The authors point out that only two reports on a total of 3 cases have appeared, lending support to the concept that the ocular motor nuclei are involved in patients with chronic progressive ophthalmoplegia. Furthermore, they state that the pathological changes in the ocular motor nuclei in these 3 cases were equivocal. Schwarz and Liu[60] also describe a patient with progressive ophthalmoplegia who had no changes in the oculomotor, trochlear or abducens nuclei but whose external ocular muscles at autopsy gave evidence of a primary muscle disorder. Beckett and Netsky[61] report a family in which muscular dystrophy was limited largely to the external ocular muscles, the disorder being present in the males in two successive generations. They express agreement with Kiloh and Nevin that "chronic nuclear ophthalmoplegia" is probably a form of ocular myopathy.

Kiloh and Nevin[59] have summarized the clinical features of ocular myopathy. It may begin at any time from infancy to over fifty years of age, the majority occurring before thirty. Males and females are equally affected, and a family history of ptosis or ophthalmoplegia is found in half the recorded cases. Ptosis is almost always the first sign, although it may fail to appear. The condition may or may not be symmetrical at the onset. The course of the disease is insidious. Slight fluctuations of ptosis may occur in relation to fatigue, but remissions are not seen. The advance of the disease may be halted temporarily or permanently at any stage. Diplopia is sometimes an early symptom, but is absent in the majority of cases because of the symmetrical development of the ocular palsy. Pupillary changes ordinarily do not occur. Hutchinsonian facies often develops in the course of the disorder. The forehead is constantly wrinkled in an effort to elevate the lids, the head is tilted back, and the droopy eyelids give the patient a sleepy expression. In about a quarter of the cases other muscular groups may be involved, these most commonly being the orbiculares oculi, the facial muscles, muscles of mastication and the sternocleidomastoid muscles. Ten per cent of the cases show involvement of muscles supplied by the spinal cord. These observers do not believe that the disorder can be rigidly separated from other types of muscular dystrophy.

Hepatolenticular Degeneration

The presence of two metabolic errors in hepatolenticular degeneration (Wilson's disease) has been firmly established. In the first place Cumings[62] has fully confirmed earlier reports describing abnormal accumulations of tissue copper and an excessive excretion of copper in the urine of patients with this disease. Secondly, increased urinary excretion of amino acids, in the absence of hepatic failure, has been demonstrated in this disorder by Uzman and Denny-Brown.[63] A rise in urinary excretion of the ten "essential" amino acids[64] and also of the "non-essential" acids, glycine and alanine,[65] has been shown to occur in the absence of an elevated serum amino nitrogen. It has been suggested that the abnormality of amino acid excretion is secondary to a failure of reabsorption of the amino acids by the renal tubules.[65] The demonstration of a generalized aminoaciduria has brought this disorder into relation with the Fanconi syndrome (vitamin D resistant rickets, or osteomalacia, and often renal glycosuria).[65] Furthermore, evidence has accumulated that both these varieties of renal aminoaciduria are hereditary abnormalities. Wilson[66] originally considered the disease described by him to be a familial condition, but after his original paper support was found for the notion that this disease is inherited through a recessive factor, and Dent and Harris[67] recently showed that the Fanconi syndrome is almost certainly inherited on the basis of recessive factors. Thus, hepatolenticular degeneration may be another example of the disorders that Garod called "inborn metabolic errors."[65]

Cumings[62] found quantities of copper in the liver in the range from 39.4 to 56.5 mg. per 100 gm. of dried tissue, in contrast with the normal range of 3.7 to 17.2 mg. per 100 gm. The basal ganglions contained copper to the extent of 69.5 to 71.6 mg. per 100 gm. of dry tissue in comparison with a normal content in the range from 6.1 to 12.0 mg. per 100 gm. Denny-Brown and Porter[68] observed that patients with Wilson's disease excreted from 207 to 713 gamma of copper per twenty-four hours in the urine, in comparison with the normal urinary excretion of 0 to 14.7 gamma. Biliary copper excretion appeared to be within normal limits, however.[63] Denny-Brown and Porter[68] reported that 2,3-dimercaptopropanol (BAL) produced a great increase in the excretion of urinary copper. This was not associated with a change in excretion of amino acids.

Serum copper values have been described as abnormally high in cases reported by Glazebrook,[69] although not all patients demonstrated an elevation of serum copper. Serum copper is almost entirely in the form of a metalloprotein complex, which Holmberg and Laurell[70] have shown to be a single pure protein, called by them caeruloplasmin. This protein is a blue globulin of molecular weight of about 151,000, each molecule containing 8 atoms of copper. Electrophoretic analysis has shown that it is an alpha globulin. Scheinberg and Gitlin[71] have observed that patients with hepatolenticular degeneration have much less caeruloplasmin in their serum than normal subjects, despite the fact that their serum copper levels may be either higher or lower than normal; the caeruloplasmin content of the serum of patients with this disorder is consistently too low to account for the total amount of copper present in the serum. The authors have presented evidence that the excess noncaeruloplasmin

copper is not freely dialyzable. They point out that other plasma proteins, including albumin and iron-containing globulins, are capable of binding copper. They suggest that the degeneration is another example of a pathologic condition related to a congenital deficiency of a specific plasma protein such as that seen in hemophilia. Uzman and Hood[72] report evidence of the excretion of abnormal amounts of peptides with terminal dicarboxylic amino acids residues in the urine of nonaffected members of families of patients with this disease. These authors suggest that the process may represent the end picture of a familial generalized metabolic disturbance engendered by deficient dicarboxylic carboxypeptidases in tissues. They point out that such an eventuality may also lead to a clarification of the unexplained presence of amino acid in the urine, since competitive reabsorption of such peptides in preference to, and to the partial exclusion of, free amino acids would result in an increased excretion of amino acid in spite of normal amino acid plasma levels. It has been suggested by Himsworth[73] and by Uzman and Hood[72] that the cirrhosis observed in hepatolenticular degeneration is the direct consequence of the chronic loss of amino acids, in accordance with the observation of the high incidence of hepatic involvement by itself in families in which one or more members are affected, as well as in the Fanconi syndrome, which is also characterized by a generalized aminoaciduria.

Elevated citric acid levels in the blood were also observed by Uzman and Hood,[72] who regard this finding as reflecting defective handling of dicarboxylic amino acids and their peptides, since the deamination products of these amino acids, oxaloacetic acid and alphaketoglutaric acid participate in the tricarboxylic acid cycle, with the formation of citric acid as an intermediate. Enrichment of citric acid, they state, suggests reduction in the rate of synthesis of other amino acids through transamination or reductive amination, thus exacerbating the loss of amino acids that is already operative through the aminoaciduria.

Denny-Brown and Porter[68] and Cumings,[74] as well as others,[75] have reported clinical improvement after the administration of BAL. Varying dosage schedules have been employed, and courses of therapy have usually been repeated.[68, 74] Fading of the Kayser–Fleischer ring has also been reported by Denny-Brown. He suggests that the development of severe forms of the disease may be prevented by detection early in its course and treatment with BAL at this stage. Uzman and Hood[72] report that 5 of the asymptomatic members of a family in which 4 siblings died as a result of hepatolenticular degeneration had persistent amino acid in the urine. With laboratory procedures capable of demonstrating the biochemical defects characteristic of this disease, despite the absence of overt clinical symptoms, and with a form of therapy that holds out hopes of forestalling the development of serious symptoms, a more optimistic approach may be taken to this hitherto untreatable neurologic disorder.

"Collagen" Diseases

The neurologic aspects of dermatomyositis have been discussed by Matthews and Burne.[23] They suggest that, from a neurologic point of view, most cases of dermatomyositis fall into one of three groups. In the first group there is a rapid onset of weakness of the proximal muscles of the limbs, with spontaneous pain, muscle tenderness and often loss of tendon reflexes. There is a strong resemblance in this group of symptoms to those of polyneuritis. The presence of florid skin lesions and of cutaneous and muscular edema may clarify the diagnosis, the authors point out, but remark that the peripheral nerves may occasionally be involved in dermatomyositis. In the second group there is gradual onset of weakness of the limbs accompanied by symptoms suggestive of bulbar palsy. Changes in voice and difficulty in swallowing may be prominent. Also, ptosis may occur. Furthermore, certain of the symptoms in this group of patients — for example, the dysphagia — may be remittent. These manifestations sometimes suggest myasthenia gravis. Further, Ragan[76] has described a case of dermatomyositis in which there appeared to be some response to prostigmine. Matthews and Burne[23] point out that muscular pains, swelling or tenderness may be present or absent and that the skin lesions may be insignificant in this second group. The third group of symptoms of dermatomyositis may simulate those of other primary muscular diseases. Thus, the disease may resemble progressive muscular dystrophy, "menopausal myotrophy" of Shy and McEachern, or the late myotrophy of Nevin. Difficulty of diagnosis is increased by the fact that no pathognomonic changes in muscles have been agreed upon by those who have studied this disorder. Despite this, Matthews and Burne believe that there is justification for considering dermatomyositis as a specific disease entity. Several claims of success with treatment with ACTH have appeared.[21]

Studies of the lupus-erythematosus (L. E.) cell in the bone marrow and the plasma L. E. phenomenon, as well as the therapeutic effectiveness of ACTH and cortisone in lupus erythematosus, have stimulated considerable interest in this disease. It has long been known that neurologic signs and symptoms and pathologic changes in the nervous system occur during the course of the disease. Glaser[77] has reported 3 cases of lupus erythematosus in which widespread lesions of the central nervous system were found. He states that since 1930 autopsies have been performed in 18 cases at the Presbyterian Hospital in New York. The central nervous system was examined in 6 cases, and numerous lesions were found in the central nervous system of 3. The lesions in the nervous system are considered to be

due to involvement of the small vessels of the arterial tree, a disseminated endarteritis. In Glaser's cases, the vascular lesions were predominantly in the gray matter of the cerebral cortex, particularly the perisulcal areas. The white matter was less frequently implicated, and then usually by extension. The changes in the brain parenchyma, which were secondary to the vascular damage, consisted of focal and disseminated areas of acute and chronic encephalomalacia, often with small cyst formation. He points out that even though the vascular supplies of the basal ganglions and brain stem were extensive, lesions in these subcortical areas were noted only infrequently and when present were only of mild degree. Despite the widespread lesions in the central nervous system in the 3 cases reported by Glaser, 2 patients presented no neurologic signs or symptoms, aside from those of terminal delirium. He points out that the neurologic symptoms that have been described include focal and generalized seizures and cranial-nerve palsies, as well as motor and sensory changes. Blindness has been reported occasionally, but it is usually regarded as the result of local retinal lesions. Manifestations of an acute toxic psychosis or delirium are frequent, especially terminally, in association with high fever or uremia, and do not necessarily indicate the presence of focal cerebral lesions.

Russell et al.[32] have reported on 7 of 28 consecutive patients with positive plasma L.E. reactions who had convulsions during the course of the disease. Two of these 7 patients had convulsions for years before the occurrence of recognizable symptoms of lupus erythematosus. The authors state that this suggests that epilepsy, when accompanied by rheumatoid arthritis, may constitute a prodromal symptom of lupus erythematosus, perhaps implying the value of a search for the L.E. cell of the bone marrow or plasma L.E. phenomenon in patients with idiopathic epilepsy. They report that the electroencephalograms of patients with lupus erythematosus are characterized by slow-wave activity, invariably more marked on one side than on the other, but without definite focal involvement. Progressive and regressive changes of the electroencephalogram may parallel relapses and remissions in this disease. They further state that cortisone and ACTH treatment produced improvement in the epileptic seizures related to lupus. It is interesting in this connection that Hoefer and Glaser[78] reported that the administration of ACTH may be accompanied by electroencephalographic changes suggesting that this compound is not of value in the treatment of patients with epilepsy.

Regeneration in Central Nervous System

From time to time in the past century, attempts to bring about central-nervous-system regeneration have been made. It is generally considered that the regenerative power of central-nervous-system tissue diminishes with advances in the phylogenetic scale and that it is entirely lacking in mammals, at least in those beyond the rodents. Much interest has been aroused by the demonstration of Windle and Chambers[79] that fever induced by Piromen and other pyrogenic agents prevented the formation of a glial barrier at the site of severance of the spinal cord in the cat and the dog, and that nerve fibers could grow through the area of severance in the animals so treated.

Confirmation of this work has appeared in a paper by Gokay and Freeman,[80] who found that rats subjected to spinal-cord transection and given Piromen at certain dosage levels recovered function more rapidly than the controls. These authors also emphasized the necessity of punctilious postoperative care of animals in which experiments on regeneration of the central nervous system are done. Gokay and Freeman were unable to find an increase in percentage of rats recovering function after spinal-cord transection when cortisone and saline solution were administered.

Reports on the value of Piromen in effecting spinal-cord regeneration in human beings have not been encouraging. Covalt and his associates[81] presented their experiences with 10 patients with transected cords, or with severe trauma to the cord as demonstrated by laminectomy, who received one or several courses of this drug in dosages recommended by Windle. Except for 1 patient in whom the sensory level dropped 1 dermatome, they found no evidence of improved function or other beneficial effects. They conclude that up to the present Piromen is not an effective therapeutic agent in spinal-cord transection or severe spinal-cord trauma in human beings. Bailey and Friedlander[82] also reported that their results in the treatment of central-nervous-system injury with this agent have not been impressive.

Poliomyelitis

In an important series of papers, Robbins and his associates[83] demonstrated that the poliomyelitis virus will propagate in cultures of extraneural tissues. Employing cellular fractionation technics, Kaplan and Melnick[84] demonstrated that the poliomyelitis virus during incubation and acute stages of infection in mice is first detectable in the cytoplasmic and subsequently in the nuclear fraction. The demonstration of poliomyelitis virus in the circulating blood after oral administration of a virus preparation has now been achieved by Horstmann,[85] Bodian[86] and Faber et al.[87] The development of a complement-fixation test for the Brunhilde, Lansing and Leon types of virus by several investigators promises to be of value in the clinical study of this disorder.[88] Faber and his co-workers[89] have found evidence for a progressive centrifugal migration of virus from the central nervous system into various peripheral ganglions and into peripheral nerves, including their distal portions. They point out that

the presence of virus in extraneural tissues is not per se referable to infection of their constituent cells but rather to infection of their supplying nerves or, in some cases, to their content of virus-bearing blood. They believe that the finding of virus in the vagus nerve may throw a light on some of the electrocardiographic changes noted in certain cases of poliomyelitis, and that the presence of virus in peripheral nerve may elucidate the etiology of localized pain and tenderness, a frequent clinical manifestation of human poliomyelitis.

Hammon and his associates[90] have reported that Red Cross gamma globulin, in an average dose of 0.14 cc. per pound of body weight, in controlled field tests in three epidemics, has been shown to give highly significant protection against paralytic poliomyelitis. They base their conclusions on 104 cases of paralytic disease occurring among approximately 55,000 children, half of whom received gamma globulin and half gelatin. The cases occurring during the first week after injection of gamma globulin were significantly modified in severity. During the next period of four weeks a high, but not complete, degree of protection was demonstrated. During the sixth to the eighth week after injection, the protection appeared to be waning and was no longer detectable after the eighth week. The authors point out the limitations of the use of gamma globulin in passive immunization, and imply the importance of the development of a vaccine. The preparation of several vaccines that promise to be of value in the control of this disease has been reported.[91, 92]

Miscellaneous Considerations

The occurrence of papilledema in the Guillain–Barré syndrome was recently discussed by several clinicians.[93] This finding has only occasionally been reported in the literature.[93] It has been stated that apparently it is either overlooked or of rare incidence[93]; the value of future reports of repeated examinations of the eyegrounds during the course of the disease in resolving this question has been emphasized.[93]

Four cases of subacute cortical cerebellar degeneration have been described by Brain, Daniel and Greenfield[94]; 3 were associated with carcinomas — of the bronchi in 2 and of the ovary in 1. These authors have reviewed the literature on this subject and report that there is a high correlation in the presence of carcinoma in patients with subacute cortical cerebellar degeneration. More than two thirds of the cases of cerebellar degeneration of this type, which ran their course in two years, were associated with carcinoma, although the existence of the neoplasm was not always clinically evident. On the other hand, the more chronic forms of cerebellar degeneration show no such correlation. The authors point out that the presence of cerebellar signs in patients with known carcinoma is sometimes erroneously attributed to metastases. In the consideration of pathogenesis, emphasis is laid on the special vulnerability of the Purkinje cells to extrinsic poisons and intrinsic metabolic disturbances. The sensitivity of peripheral nerves to these factors is also well known, and, in this connection, it is perhaps instructive to recall that peripheral neuritis has been described as occurring in association with carcinoma, especially of the bronchi.[95]

Forty-five cases of cervical arthritis have been studied by Brain et al.[96] In 38 cases the spinal cord was compressed; in the remaining 7 the nerve roots only were involved. The authors state that their clinical experience has shown that cervical arthritis is a far commoner cause of symptoms and, indeed, of disabilities than is usually thought. They point out that this condition can simulate multiple sclerosis, amyotrophic lateral sclerosis, tumor of the spinal cord, syringomyelia, subacute combined degeneration and any other condition causing progressive spastic paraplegia, as well as disorders producing radicular or even brachial-plexus or peripheral-nerve symptoms. They also emphasize that since cervical arthritis is not uncommon after middle life, and may be symptomless, there is a danger that the discovery of cervical arthritis on radiography may lead to the mistaken attribution of these symptoms to this disorder when another disease is actually present. When any doubt arises, cervical arthritis should not be accepted as responsible for symptoms attributable to lesions of the spinal cord unless myelography demonstrates a protrusion of one or more intervertebral disks sufficient to cause a substantial reduction in the subarachnoid space of the spinal cord.

Subdural lesions as a complication of meningitis have received much attention recently. Three main types occur: subdural empyema, subdural effusion and subdural hemorrhage.[97] Subdural empyema occurs most frequently in meningitis due to the pneumococcus and *Haemophilus influenzae*.[97] Smith[97] found 3 positive cultures from purulent material obtained from the subdural space in 43 patients with acute bacterial meningitis on whom subdural taps were performed. He states that ordinarily the symptoms of subdural empyema in infants do not differ from those present in nonsuppurative subdural effusions, but that occasionally an area of localized inflammation presents itself over the anterior fontanelle. McKay and his associates[98] and Smith[97] have described the occurrence of sterile subdural effusions as a complication of meningitis. Matson[99] reports that roughly 50 to 60 per cent of infants under one year convalescent from meningitis have more than the normal amount of fluid in the subdural space. These effusions occur frequently in meningitis due to *H. influenzae*, sometimes in pneumococcal meningitis and occasionally in meningococcal and never in tuberculous meningitis.[97] Such effusions may lead to persistent fever (after the

spinal fluid becomes sterile), convulsions, focal neurologic signs, opisthotonos, bulging fontanelle and projectile vomiting.[97] Frequently, the infant continues to look "puny" when one would expect him, from the bacteriologic findings, to begin to "perk up." The presence of some of the foregoing symptoms is considered as indicating the advisability of exploratory subdural taps. Smith[97] states that in almost all cases subdural taps alone constitute adequate therapy, and that the effusions usually clear in not more than three weeks. Matson[99] has declared that if effusions are not eliminated by a few subdural taps, it is important to explore surgically for the presence of encapsulating membranes, and that if these are found, they should be removed. He states that studies of approximately 70 infants with postmeningitis subdural effusions indicate that the incidence of permanent neurologic sequelae can be greatly reduced by proper treatment of this complication. Subdural hemorrhage has been reported only as a complication of meningococcal meningitis.[97] Smith[97] states that only 3 reports of this disorder, each describing a single patient, have so far appeared.

Biochemical studies on 26 patients with hepatolenticular degeneration have been described by Bearn[100] since this paper was submitted for publication. Serum copper levels were determined in 17 cases and were low in 15. A lowered caeruloplasmin level was observed in all cases. Bearn believes that these findings are characteristic of the disease and are not found in patients with other forms of liver disease, in whom serum copper and caeruloplasmin levels are frequently elevated.

Results of analyses of the urines of 6 patients with hepatolenticular degeneration by means of ion-exchange columns were recently reported by Moore and Stein.[101] They report increase in excretion of many of the amino acids normally present in the urine, although excretions of taurine, aspartic acid, isoleucine methyl histidine and arginine were in amounts close to normal range. Proline and citrulline, not found in normal urine, were frequently present.

References

1. Walshe, R. M. R. On interpretation of experimental studies of cortical motor function: with special reference to "operational view" of experimental procedures. *Brain* **74**:249-266, 1951.
2. Liddell, E. C. T., and Phillips, C. G. Overlapping areas in motor cortex of baboon. *J. Physiol.* **112**:392-399, 1951.
3. Woolsey, C. N., et al. Patterns of localization in precentral and "supplementary" motor areas and their relation to concept of premotor area. *Proc. A. Res. Nerv. & Ment. Dis.* **30**:238-264, 1952.
4. Penfield, W., and Rasmussen, T. *The Cerebral Cortex of Man: A clinical study of localization of function.* 248 pp. New York: Macmillan, 1950.
5. Sloan, N., and Jasper, H. Identity of spreading depression and "suppression." *Electroencephalog. & Clin. Neurophysiol.* **2**:59-78, 1950.
6. Marshall, W. H., and Essig, C. F. Relation of air exposure of cortex to spreading depression of Leão. *J. Neurophysiol.* **14**:265-273, 1951.
7. Marshall, W. H., Essig, C. F., and Dubroff, S. J. Relation of temperature of cerebral cortex to spreading depression of Leão. *J. Neurophysiol.* **14**:153-166, 1951.
8. Leão, A. A. P., and Morison, R. S. Propagation of spreading cortical depression. *J. Neurophysiol.* **8**:33-45, 1945.
9. Penfield, W., and Kristiansen, K. *Epileptic Seizure Patterns: A study of localizing value of initial phenomena in focal cortical seizures.* 104 pp. Springfield, Illinois: Thomas, 1951.
10. Feindel, W., Penfield, W., and Jasper, H. Localization of epileptic discharge in temporal lobe automatism. *Tr. Am. Neurol. A.* **77**: 14-16, 1952.
11. Gibbs, E. L., and Gibbs, F. A. Electroencephalographic change with age during sleep. *Electroencephalog. & Clin. Neurophysiol.* **1**:355, 1949.
12. Jasper, H., and Penfield, W. Electroencephalographic studies of epileptic automatisms. Presented at a meeting of the American Psychiatric Association, Montreal, Quebec. May 23-27, 1949.
13. Ajmone-Marsan, C., and Stoll, J. Subcortical connections of temporal pole in relation to temporal lobe seizures. *Arch. Neurol. & Psychiat.* **66**:669-686, 1951.
14. *Idem.* Experimental studies of epileptic discharges in anterior temporal regions of monkey. *Electroencephalog. & Clin. Neurophysiol.* **3**:377, 1951.
15. Ajmone-Marsan, C., Stoll, J., and Jasper, H. H. Electrophysiological studies of subcortical connections of tip of temporal lobe. *Electroencephalog. & Clin. Neurophysiol.* **2**:356, 1950.
16. Stoll, J., Ajmone-Marsan, C., and Jasper, H. H. Electrophysiological studies of subcortical connections of anterior temporal region in cat. *J. Neurophysiol.* **14**:305-316, 1951.
17. Penfield, W., and Flanigin, H. Surgical therapy of temporal lobe seizures. *Tr. Am. Neurol. A.* **75**:146-149, 1950.
18. Magoun, H. W. Caudal and cephalic influences of brain stem reticular formation. *Physiol. Rev.* **30**:459-474, 1950.
19. Ward, A. A., Jr., McCulloch, W. S., and Magoun, H. W. Production of alternating tremor at rest in monkeys. *J. Neurophysiol.* **11**: 317-330, 1948.
20. Ward, A. A., Jr., and Jenkner, F. L. Bulbar reticular formation and tremor. Presented at a meeting of the American Neurological Association, Atlantic City, New Jersey, June 16, 1953.
21. Merritt, H. H. Corticotropin and cortisone in diseases of nervous system. *Yale J. Biol. & Med.* **24**:466-473, 1952.
22. Rothendler, H. H. Bell's palsy treated with cortisone. *J. Nerv. & Ment. Dis.* **114**:346-376, 1951.
23. Matthews, W. B., and Burne, J. C. Neurological aspects of dermatomyositis. *J. Neurol., Neurosurg. & Psychiat.* **16**:49-55, 1953.
24. Shy, G. M., and McEachern, D. Further studies on effects of cortisone and ACTH on neurological disorders. *Brain* **74**:354-362, 1951.
25. Milhorat, A. T. Effect of ACTH in myotonia atrophica and in progressive muscular dystrophy. In *Proceedings of the First Clinical ACTH Conference.* Edited by J. R. Mote. 607 pp. Philadelphia: Blakiston, 1950. Pp. 588-594.
26. Glaser, G. H., and Merritt, H. H. Effects of corticotropin (ACTH) and cortisone on disorders of nervous system. *J. A. M. A.* **148**: 898-904, 1952.
27. Reese, H. H., and Peters, H. A. Therapeutic effects of ACTH in myotonia dystrophica. *Dis. Nerv. System* **13**:99-105, 1952.
28. Stillmann, J. S., and Ganong, W. F. Guillain-Barré syndrome: report of case treated with ACTH and cortisone. *New Eng. J. Med.* **246**:293-296, 1952.
29. Seltzer, H. S., Lichty, D. E., and Conn, J. W. Case of Guillain-Barré syndrome (infectious polyneuritis) with apparent response to ACTH. *Univ. Mich. M. Bull.* **18**:27-31, 1952.
30. Forsham, P. H. Discussion of Glaser, G. H., Merritt, H. H., and Traeger, C. H. Effect of pituitary adrenocorticotrophic hormone (ACTH) on multiple sclerosis: preliminary report. In *Proceedings of the Second Clinical ACTH Conference.* Edited by J. R. Mote. 716 pp. Philadelphia: Blakiston, 1951. Pp. 145-147.
31. Klein, R., and Livingston, S. Effect of adrenocorticotropic hormone in epilepsy. *J. Pediat.* **37**:733-742, 1950.
32. Russell, P. W., Haserick, J. R., and Zucker, E. M. Epilepsy in systemic lupus erythematosus: effect of cortisone and ACTH. *Arch. Int. Med.* **88**:78-92, 1951.
33. Aronson, N., Douglas, H. S., and Lewis, J. M. Cortisone in Sydenham's chorea: report of 2 cases. *J. A. M. A.* **145**:30-33, 1951.
34. Schwarz, H. Chorea gravis (Sydenham's chorea) treated with cortisone and ascorbic acid. *Canad. M. A. J.* **65**:150, 1951.
35. Egas Moniz. L'encéphalographie artérielle, son importance dans la localisation des tumeurs cérébrales. *Rev. neurol.* **2**:72-90, 1927.
36. Lima, P. A. *Cerebral Angiography.* 221 pp. London: Oxford Press, 1950.
37. Torkildsen, A. Carotid angiography with special reference to diagnosis of cerebral gliomas. *Acta psychiat. et neurol.* Supp. **55**:3-168, 1949.
38. Ecker, A. *The Normal Cerebral Angiogram.* 190 pp. Springfield, Illinois: Thomas, 1951.
39. Hamby, W. B. *Intracranial Aneurysms.* 564 pp. Springfield, Illinois: Thomas, 1952.
40. Bull, J. W. D. Diagnostic neuroradiology. In *Modern Trends in Neurology.* 717 pp. Edited by A. Feiling. New York: Hoeber, 1951. Pp. 600-669.
41. Curtis, J. B. Rapid serial angiography: preliminary report. *J. Neurol., Neurosurg. & Psychiat.* **12**:167-182, 1949.
42. Sugar, O., Holden, L. B., and Powell, C. B. Vertebral angiography. *Roentgenol.* **61**:166-182, 1949.
43. Krayenbuhl, H. Immediate and late results of carotid ligature in intracranial aneurysms. *Schweiz. med. Wchnschr.* **76**:908-914, 1946.
44. Alpers, B. J., and Ryan, J. J. Verified cerebral aneurysm with negative arteriogram. *J. Nerv. & Ment. Dis.* **109**:220-225, 1949.
45. Amador, L., Bailey, P., Harrison, L. R., Sugar, O., and Walker, A. E. Angiographic diagnosis of intracranial neoplasms. *Tr. Am. Neurol. A.* **77**:137-140, 1952.

46. Dunsmore, R. H., Scoville, W. B., and Whitcomb, B. B. Complications of angiography. *J. Neurosurg.* **8**:110-118, 1951.

47. Foltz, E. L., Thomas, L. B., and Ward, A. A., Jr. Effects of intracarotid Diodrast. *J. Neurosurg.* **9**:68-82, 1952.

48. Gowers, W. R. *A Manual of Diseases of the Nervous System: Diseases of the nerves and spinal cord.* 675 pp. Vol. I. Third edition. Philadelphia: Blakiston, 1899.

49. Hunt, J. R. Role of carotid arteries in causation of vascular lesions of brain: with remarks on certain special features of symptomatology. *Am. J. M. Sc.* **147**:704-713, 1914.

50. Egas Moniz, Lima, A., and de Lacerda, R. Hémiplégies par thrombose de la carotide interne. *Presse méd.* **45**:977-980, 1937.

51. Cloake, P. C. P. Thrombosis of internal carotid artery. In *Modern Trends in Neurology.* 717 pp. Edited by A. J. Feiling. New York: Hoeber, 1951. Pp. 466-493.

52. Denny-Brown, D. Symposium on specific methods of treatment: treatment of recurrent cerebrovascular symptoms and question of "vasospasm." *M. Clin. North America* **35**:1457-1474, 1951.

53. *Idem.* Changing pattern of neurologic medicine. *New Eng. J. Med.* **246**:839-846, 1952.

54. Wilson, G., Rupp, C., Jr., Riggs, H. E., and Wilson, W. W. Factors influencing development of cerebral vascular accidents: role of cardiocirculatory insufficiency. *J. A. M. A.* **145**:1227-1239, 1951.

55. Levene, P. A., and Kristeller, L. Factors regulating creatinin output in man. *Am. J. Physiol.* **24**:45-65, 1909.

56. Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry.* Vol. I. 1041 pp. Second edition. Baltimore: Williams & Wilkins, 1946.

57. Sandberg, A. A., Hecht, H. H., and Tyler, F. H. Studies in disorders of muscle. X. Site of creatine synthesis in human. *Metabolism* **2**:22-29, 1953.

58. Roche, M., Benedict, J. D., Yü, T. F., Bien, E. J., and Stetten, DeW., Jr. Origin of urinary creatine in progressive muscular dystrophy. *Metabolism* **1**:13-19, 1952.

59. Kiloh, L. G., and Nevin, S. Progressive dystrophy of external ocular muscles (ocular myopathy). *Brain* **74**:115-143, 1951.

60. Schwarz, G. A., and Liu, C-N. Chronic progressive external ophthalmoplegia. *Tr. Am. Neurol. A.* **78**:143, 1953.

61. Beckett, R. S., and Netsky, M. G. Familial ocular myopathy and external ophthalmoplegia. *Arch. Neurol. & Psychiat.* **69**:64-72, 1953.

62. Cumings, J. N. Copper and iron content of brain and liver in normal and in hepato-lenticular degeneration. *Brain* **71**:410-415, 1948.

63. Uzman, L., and Denny-Brown, D. Amino-aciduria in hepatolenticular degeneration (Wilson's disease). *Am. J. M. Sc.* **215**:599-611, 1948.

64. Cooper, A. M., Eckhardt, R. D., Faloon, W. W., and Davidson, C. S. Investigation of aminoaciduria in Wilson's disease (hepatolenticular degeneration): demonstration of defect in renal function. *J. Clin. Investigation* **29**:265-278, 1950.

65. Matthews, W. B., Milne, M. D., and Bell, M. Metabolic disorder in hepato-lenticular degeneration. *Quart. J. Med.* **21** N.S.: 425-446, 1952.

66. Wilson, S. A. K. Progressive lenticular degeneration: familial nervous disease associated with cirrhosis of liver. *Brain* **34**:295-509, 1912.

67. Dent, C. E., and Harris, H. Genetics of "cystinuria." *Ann. Eugenics* **16**:60-87, 1951.

68. Denny-Brown, D., and Porter, H. Effect of BAL (2,3-dimercaptopropanol) on hepatolenticular degeneration (Wilson's disease). *New Eng. J. Med.* **245**:917-925, 1951.

69. Glazebrook, A. J. Wilson's disease. *Edinburgh M. J.* **52**:83-87, 1945.

70. Holmberg, C. G., and Laurell, C. B. Investigations in serum copper. I. Nature of serum copper and its relation to iron-binding protein in human serum. *Acta chem. Scandinav.* **1**:944-950, 1947.

71. Scheinberg, I. H., and Gitlin, D. Deficiency of ceruloplasmin in patients with hepatolenticular degeneration (Wilson's disease). *Science* **116**:484, 1952.

72. Uzman, L. L., and Hood, B. Familial nature of amino-aciduria of Wilson's disease (hepatolenticular degeneration). *Am. J. M. Sc.* **223**:392-400, 1952.

73. Himsworth, H. P. *Lecture on Liver and Its Diseases.* Second edition. 222 pp. Cambridge: Harvard University Press, 1950.

74. Cumings, J. N. Effects of B.A.L. in hepatolenticular degeneration. *Brain* **74**:10-22, 1951.

75. Streifler, M., and Feldman, S. Effect of dimercaprol (BAL) in hepatolenticular degeneration: report of case, with clinical and electroencephalographic study. *Arch. Neurol. & Psychiat.* **69**: 84-90, 1953.

76. Ragan, C. Effect of adrenocorticotrophic hormone (ACTH) (Armour) on clinical syndrome of dermatomyositis. In *Proceedings of the First Clinical ACTH Conference.* Edited by J. R. Mote. 607 pp. Philadelphia: Blakiston, 1950. Pp. 423-428.

77. Glaser, G. H. Lesions of central nervous system in disseminated lupus erythematosus. *Arch. Neurol. & Psychiat.* **67**:745-753, 1952.

78. Hoefer, P. F. A., and Glaser G. H. Effects of pituitary adrenocorticotropic hormone (ACTH) therapy: electroencephalographic and neuropsychiatric changes in fifteen patients. *J. A. M. A.* **143**:620-624, 1950.

79. Windle, W. F., and Chambers, W. W. Regeneration in spinal cord of cat and dog. *J. Comp. Neurol.* **93**:241-257, 1950.

80. Gokay, H., and Freeman, L. W. Drugs and spinal cord regeneration. *Quart. Bull. Indiana Univ. Med. Center* **14**:67-69, 1952.

81. Covalt, D. A., Cooper, I. S., Hoen, T. I., and Rusk, H. A. Early management of patients with spinal cord injury. *J. A. M. A.* **151**:89-94, 1953.

82. Bailey, P., and Friedlander, W. J. The use of Piromen in central nervous system injury: preliminary survey. Presented at the Fifth Annual Meeting of the American Academy of Neurology. Chicago, Illinois, April 9, 1953.

83. Robbins, F. C., Enders, J. F., Weller, T. H., and Florentino, G. L. Studies on cultivation of poliomyelitis viruses in tissue culture. V. Direct isolation and serologic identification of virus strains in tissue culture from patients with nonparalytic and paralytic poliomyelitis. *Am. J. Hyg.* **54**:286-293, 1951.

84. Kaplan, A. S., and Melnick, J. L. Intracellular localization of poliomyelitis virus. *J. Exper. Med.* **97**:91-117, 1953.

85. Horstmann, D. M. Poliomyelitis virus in blood of orally infected monkeys and chimpanzees. *Proc. Soc. Exper. Biol. & Med.* **79**: 417-419, 1952.

86. Bodian, D. Reconsideration of pathogenesis of poliomyelitis. *Am. J. Hyg.* **55**:414-438, 1952.

87. Faber, H. K., Silverberg, R. J., and Dong, L. Studies on entry and egress of poliomyelitic infection. V. Entry after single feeding: with notes on viremia. *J. Exper. Med.* **97**:69-75, 1953.

88. Svedmyr, A., Enders, J. F., and Holloway, A. Complement fixation with three types of poliomyelitis viruses propagated in tissue culture. *Am. J. Hyg.* **57**:60-70, 1953.

89. Faber, H. K., Silverberg, R. J., and Dong, L. Studies on entry and egress of poliomyelitic infection. VI. Centrifugal spread of virus into peripheral nerve: with notes on its possible implications. *J. Exper. Med.* **97**:455-465, 1953.

90. Hammon, W. McD., Coriell, L. L., Wehrle, P. F., and Stokes, J., Jr. Evaluation of Red Cross gamma globulin as prophylactic agent for poliomyelitis. 4. Final report of results based on clinical diagnosis. *J. A. M. A.* **151**:1272-1285, 1953.

91. Salk, J. E., Bennett, B. L., Lewis, L. J., Ward, E. N., and Younger, J. S. Studies in human subjects on active immunization against poliomyelitis. 1. Preliminary report of experiments in progress. *J. A. M. A.* **151**:1081-1098, 1953.

92. Howe, H. A. Antibody response of chimpanzees and human beings to formalin-inactivated trivalent poliomyelitis vaccine. *Am. J. Hyg.* **56**:265-286, 1952.

93. Drew, A. L., and Magee, K. R. Papilledema in Guillain-Barré syndrome. *Arch. Neurol. & Psychiat.* **66**:744-751, 1951.

94. Brain, W. R., Daniel, P. M., and Greenfield, J. G. Subacute cerebellar degeneration and its relations to carcinoma. *J. Neurol., Neurosurg. & Psychiat.* **14**:59-75, 1951.

95. Wybourn-Mason, R. Bronchial carcinoma presenting as polyneuritis. *Lancet* **1**:203-206, 1948.

96. Brain, W. R., Northfield, D., and Wilkinson, M. Neurological manifestations of cervical spondylosis. *Brain* **75**:187-225, 1952.

97. Smith, M. H. D. Infection and subdural space. *Bull. Tulane M. Fac.* **12**:105-107, 1953.

98. McKay, R. J., Morissette, R. A., Ingraham, F. D., and Matson, D. D. Collections of subdural fluid complicating meningitis due to *Haemophilus influenzae* (type B). *New Eng. J. Med.* **242**:20, 1950.

99. Matson, D. D. Subdural effusion complicating bacterial meningitis in infants. *Tr. Am. Neurol. A.* **78**:123, 1953.

100. Bearn, A. G. Genetic and biochemical aspects of Wilson's disease. *Am. J. Med.* **15**:442-449, 1953.

101. Moore, S., and Stein, W. H. Aminoacidiuria in Wilson's disease. In *Proceedings of the Industrial International Congress of Biochemistry.* 510 pp. Paris: Laumier, 1952. Pp. 367 and 368.

MEDICAL INTELLIGENCE

THE DETECTION OF SPLENOMEGALY BY PERCUSSION*

ROBERT K. NIXON, JR., M.D.†

CHICAGO

IN an age when ever more refined laboratory tests are the keynote, it may seem anachronistic to describe again a simple method in bedside diagnosis. Since evaluation of splenomegaly still rests for the most part on physical examination however, it is believed that a technic often heretofore neglected in classic teaching should merit consideration.

Percussion as an aid in determining the presence of an enlarged spleen is mentioned only in passing in all the modern standard works on physical diagnosis. The consensus has been that the method is of little value because of interfering tympany resulting from contiguous structures — namely, the stomach and colon.[1-9] This is true if the patient is examined in the supine position since the spleen lies posteriorly and may be overlapped anteriorly and laterally by bowel. However, in most discussions the authors fail to mention percussion in other than the supine position. The only exceptions are found in older treatises,[10-12] particularly that of Guttmann,[12] which gives a complete description of percussion of the spleen in various positions.

It is believed that the method described below obviates interference by air-containing viscera in outlining splenic dullness and as such deserves emphasis as an integral part of the physical examination of the spleen.

METHOD

The patient is placed in the right lateral recumbent position with the left arm extended forward and upward sufficiently to clear the left lower part of the thorax. In this position the spleen lies above both stomach and colon, permitting determination of its upper and lower borders of dullness. After palpation for the lower border on inspiration, percussion is initiated at the lower level of pulmonary resonance in approximately the posterior axillary line and carried downward obliquely on a general perpendicular line toward the lower midanterior costal margin. Normally, the upper border of dullness is measured 6 to 8 cm. above the costal margin. Dullness increased over 8 cm. is indicative of splenic enlargement in the adult (Fig. 1).

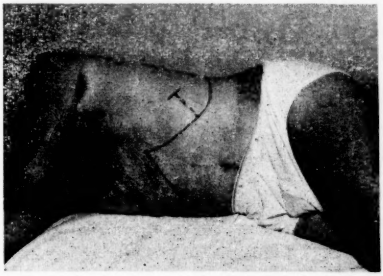

FIGURE 1. *Normal Limits of the Upper Border of Splenic Dullness, with Reference to the Costal Margin.*

DISCUSSION

The spleen may be said to be the crucial point in the diagnosis of many systemic diseases. Its pivotal importance is underlined by consideration of the great number of pathologic conditions in which awareness of splenomegaly provides a clue to the eventual outcome. When grossly enlarged the organ is usually palpable by even the most inexperienced examiner, and percussion of its borders is for the most part unnecessary. Frequently, however, a minimally enlarged spleen makes palpation difficult, particularly in patients with muscular, poorly relaxed abdominal walls. Moreover, in the patient who is unable to co-operate by inspiring deeply for palpation splenomegaly may be overlooked if percussion by the technic outlined above is not utilized. Finally, in the differentiation of other left-upper-quadrant masses arising retroperitoneally — such as the kidney and tumors — percussion in the right lateral recumbent position invariably produces tympany at the costal margin, in contrast to the dullness attendant on splenic enlargement.

That the method presented above for outlining splenic size is valid has been confirmed in my experience by successful splenic aspiration biopsies in 60 cases. A considerable number were performed on spleens in which the lower edge was barely palpable, requiring accurate appraisal of the upper border for the intracostal approach.

Percussion of the spleen is offered in no way as a maneuver to replace examination by palpation. On the contrary, it is suggested only as a supplementary and confirmatory measure. It is believed that the routine employment of both palpation and percussion in the position described will materially aid in the detection of splenomegaly.

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References

1. Cabot, R. C., and Adams, F. D. *Physical Diagnosis.* Thirteenth edition. 888 pp. Baltimore: Wood, 1942. P. 622.
2. Kampmeier, R. H. *Physical Examination in Health and Disease.* 821 pp. Philadelphia: Davis, 1950. P. 572.
3. Freilich, E. B., and Coe, G. C. *Manual of Physical Diagnosis, With Special Consideration of the Heart and Lungs.* Third edition. Revised with the collaboration of J. K. Freilich. 351 pp. Chicago: Year Book Publishers, 1947. P. 303.
4. Brust, R. W. *Physical Diagnosis.* 294 pp. New York: Appleton-Century-Crofts, 1951. P. 227.
5. Walker, H., et al. *Physical Diagnosis.* 461 pp. St. Louis: Mosby, 1952. P. 201.
6. Sutton, D. C. *Physical Diagnosis: The art and technique of history taking and physical examination of the patient in health and in disease.* 495 pp. St. Louis: Mosby, 1937. P. 407.
7. Major, R. H. *Physical Diagnosis.* Fourth edition. 446 pp. Philadelphia: Saunders, 1951. P. 322.
8. *Medical Diagnosis: Applied physical diagnosis.* Second edition. Edited by R. L. Pullen. 1119 pp. Philadelphia: Saunders, 1950. P. 603.
9. Chamberlain, E. N. *Symptoms and Signs in Clinical Medicine: An introduction to medical diagnosis.* Fourth edition. 463 pp. Baltimore: Wood, 1947. P. 209.
10. Elmer, W. P., and Rose, W. D. *Physical Diagnosis.* Seventh edition. 919 pp. St. Louis: Mosby, 1935. P. 396.
11. Gibson, G. A., and Russell, W. *Physical Diagnosis.* Revised and rewritten by F. R. Boyd. Third edition. 448 pp. New York: Appleton, 1902. P. 212.
12. Guttmann, P. *Handbook of Physical Diagnosis. Comprising Throat, Thorax, and Abdomen.* 344 pp. New York: Wood, 1880. P. 265.

BY THE LONDON POST

Clinical Research—Cleaner Food—In Quest of Health

JOHN LISTER, M.D.

LONDON, ENGLAND

THE crucial word in medicine today seems to be research. Any aspirant to a senior clinical post is expected to give an account of his research experience and to have a list of published papers to his credit; any doctor whose activities seem mysterious to his colleagues is surely engaged on a research project, and indeed many a medical husband who habitually returns home late protests that he has been detained in the research laboratory. Facetious though these remarks may be, it is worth while to consider the trends of medical research in recent years.

One of the side effects of the National Health Service was an initial sharpening of the division between the teaching and the nonteaching hospitals and, to a lesser extent, between the university professorial staff and the clinical staff within the teaching hospitals. The division was partly due to administrative circumstances, the professorial staff being employed by the universities and the clinicians by the Health Service. Since the responsibility of the medical schools is chiefly the teaching of medicine and the furtherance of knowledge and that of the National Health Service chiefly the care of the sick, it is easy to understand how research became largely concentrated in the hands of the professors and their minions. Nor can it be disputed that these professional investigators are best equipped by virtue of their training and vocation for the pursuit of modern research with its physical, chemical, physiologic and biologic approach. Hence they have had at their disposal the bulk of the available research funds, both from university sources and from the Medical Research Council. The great emphasis on technical procedure and the complexity of many contemporary scientific papers have perhaps in themselves been responsible for a revival of interest in the possibilities of simple clinical observation. Sir James Spence, professor of child health in the University of Durham, discussing this aspect of clinical science earlier this year, stated that hindrance to clinical research lies less in the claims of other clinical responsibilities than in the prevailing attitude to it. This begins in the medical school, where the undergraduate thinks of medical research only as an affair of animal experiment and laboratories. Sir James deplored this attitude and said that many present-day textbook descriptions of disease are inaccurate and inadequate. He stressed the need for accurate bedside recording of disease and of long-term, planned clinical studies.

Recognizing the need for encouraging such work, the Minister of Health recently proposed that a clinical research board be set up within the framework of the Medical Research Council. Such a board has now been formed and under the chairmanship of Sir Geoffrey Jefferson, F.R.S., it will be concerned with promoting clinical research on a national basis. It is hoped that this research will be as free as possible from detailed supervision and that some form of clinical investigation will become as much a part of the consultant's duty as the routine care of patients. The data collected in this way should eventually complement the more strictly scientific work that will continue to be concentrated in the teaching centers.

Plans for clinical research on a smaller scale are also under way. Many hospitals, after the State took over, found that certain endowment monies did not pass to the Minister's purse, and these funds have been made available for limited research projects. The outstanding example has been the foundation of a new institute of clinical research at the Middlesex Hospital. Research workers will be appointed to work in the institute for a prescribed term, and each will be sponsored by one of the Middlesex consultants. The accommodation includes comfortable consulting rooms, waiting rooms and a conference room. Laboratory facilities, x-ray plant and an animal house are also available, together with rooms for individual research workers. The institute is under the direction of Professor Alan Kekwick, and it is hoped that the work done there will help to bridge the gap between the doctor in the laboratory and the doctor in the ward.

* * *

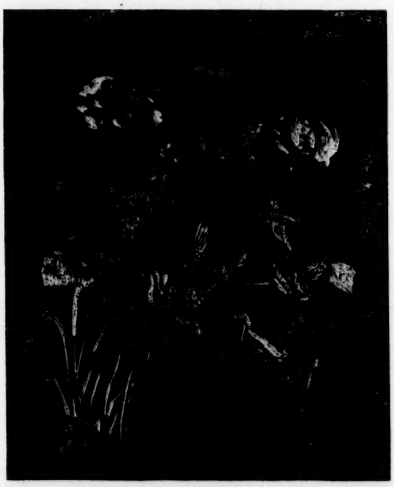
Visitors to Britain, who not only have suffered dyspepsia on account of the "good solid food" but also have perhaps been somewhat appalled by the

apparently low standards of hygiene in some cafés and by the sale of unwrapped foods in stores, will be interested to hear that a clean-food bill has just been introduced in Parliament. The purpose of this legislation, officially called the Food and Drugs Amendment Bill, is to campaign for clean, safe food. The Bill gives power to the ministers of health and food to make regulations covering the whole field of food hygiene, including the construction, equipment and cleanliness of premises, the use of materials and the inspection of meat. The Minister of Food is given power to obtain full information about any new substance intended for use in the preparation of food and to prohibit the sale of food made injurious to health by "addition, abstraction or other process." The Bill also makes it an offense for a manufacturer to make misleading claims about the nutritional value of a food either on labels or in advertisements.

The *Lancet*, in a leading article, points out that good though the aims of this Bill may be, the success of the plans to make dirty food a thing of the past will depend on the public: the education of food handlers and manufacturers will never progress so long as the public remains apathetic to such an insult to laws of hygiene as that offered by a careless butcher, "digging his hands into a bowl of mince or a confectioner using her fingers to pick chocolates out of a box."

* * *

Similar emphasis on the citizens' duty in the quest for health was laid by Sir John Charles, chief medical officer of the Ministry of Health, in his report on the nation's health in 1952. He urged that more attention be paid to simple rules of diet, exercise, relaxation and rest, and he mentioned "sorry tales of parental carelessness." He said that even breast-fed babies might not get enough nourishment to make up for Britain's gray skies. Yet only half the available orange juice and codliver oil was being taken up at welfare centers. Infant vaccinations against smallpox were 70 per cent less than they ought to be. Not nearly enough mothers were attending the child welfare centers, and full use was not being made of dental facilities and school medical services. He also thought that something must be far wrong when more children under fifteen died of accidents in the home than on the congested roads. He said it was the function of the State to arrange preventive and curative medicine. It is no less the responsibility of the individual to practice the principles on which bodily and mental health depend.



MASSACHUSETTS PHYSICIANS ART ASSOCIATION

22. *A Study in Copper*

Exhibited at Massachusetts Medical Society Annual Meeting, 1953

Hammered Copper by
JACOB W. HITE

Medical Staff, Massachusetts Women's Hospital

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40041

PRESENTATION OF CASE

A twenty-one-year-old college student was admitted to the hospital because of jaundice.

The patient had been well until about eight months previously, when nausea, a bloated sensation and some vomiting began. He did not have fever but experienced chilly sensations. He began to have frequent light-colored stools and became jaundiced. A barium-enema examination was said to have shown an "irritated colon"; he felt weak and tired ten days after the onset of symptoms and was admitted to another hospital, where positive physical findings included jaundice, a liver edge 1 finger-breadth below the right costal margin and some tenderness in the right upper quadrant. At this time the temperature was 99.8°F., the pulse 100, the respirations 24, and the blood pressure 150 systolic, 94 diastolic. In the other hospital urinalyses were negative except for a ++++ test for bile; +++ to ++++ tests for bile continued throughout the hospital stay, which lasted about a month. Urinary urobilinogen was positive in a dilution of 1:10. The blood hemoglobin was 16.0 gm. per 100 cc., and the white-cell counts ranged from 8500 to 13,500. On admission the differential count was 42 per cent neutrophils, 47 per cent lymphocytes, 5 per cent monocytes, 4 per cent eosinophils and 2 per cent basophils with a question whether some of the lymphocytes were atypical. Subsequently, the differential count was 60 per cent neutrophils and 32 per cent lymphocytes, "atypical lymphocytes being ++." The serum bilirubin, which was 12.1 mg. per 100 cc. on admission, gradually decreased to 3.4 mg. per 100 cc. on discharge. The serum total protein was 8.8 gm., the albumin 5.1 gm., and the globulin 3.7 gm. per 100 cc. The alkaline phosphatase was 5.8 units on admission, rose to 6.4 units and fell to 4.8 units per 100 cc. at the time of discharge. Phosphorus levels were 5.2 mg. and 4.2 mg. per 100 cc. Cephalin flocculation was ++ on discharge. Thymol turbidity was 6.7 units on admission, gradually decreasing to 3.6 units per 100 cc. The prothrombin time was 74 per cent of normal on entry and 100 per cent on discharge. Heterophil-antibody agglutination shortly after admission was ++++ at 1:20 and 1:40, +++ at 1:80, ++ at 1:160 and + at 1:320; a subsequent determination was ++++ at 1:20, +++ at 1:40, + at 1:80 and negative at 1:160 and 1:320. A plain film of the abdomen two days after entry did not reveal anything abnormal. In a cholecystogram about four weeks after admission the gall bladder was not visualized, and no definite opaque stones were seen in the region of the gall bladder. A barium-enema examination two days later showed probable chronic superficial colitis without evidence of ulceration; changes were most marked in the right transverse colon and in the rectosigmoid. There was some calcification in the region of the head of the pancreas; however, this observation was not enlarged upon. The patient was treated with a 3500-calorie, low-residue diet and vitamins. Liver-function studies slowly returned to normal but were not completely normal even on discharge, thirty-five days after admission. The symptoms gradually disappeared, and he returned to college five months before admission to this hospital. He apparently did well until three or four weeks before admission, when he again noted loss of energy and increased perspiration. Four days later dark urine and light stools returned. Within two days, however, the stools were dark again although the urine continued to be slightly dark. His physician found him to be jaundiced, and did blood tests, which were said to be abnormal. On the advice of his physician he stayed in bed for a week, returning to college at the end of that time for class examinations. He had only slight itching. He did not have fever or chills, vomiting, abdominal pain or return of light stools. Although his appetite was possibly slightly poorer, he was hungry before meals and ate well.

He denied exposure to any jaundiced person in the past.

Physical examination showed a moderately obese and icteric man in no distress. There were areas of dark-brown pigmentation over the fingers, toes, genitalia and elbows, and groups of small vesicles over the lateral and medial aspects of the hands, some of which had been broken, leaving dry crusts. There was an ulcer, 0.2 cm. wide and 0.1 cm. deep, on the scrotum. No spider angiomas were noted; there was no lymphadenopathy. The lungs were clear. There was a soft, Grade 1 systolic murmur that was loudest at the base; otherwise, the heart was normal. The abdomen was obese and difficult to palpate. Neither liver nor spleen was palpable, although there was a suggestion of fullness in the left flank. There was also slight tenderness in both upper quadrants, and less tenderness in the epigastrium. Examination of the rectum and genitalia was negative.

The temperature was 98°F., the pulse 100, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

Urinalysis disclosed a specific gravity of 1.030, negative tests for albumin, sugar and diacetic acid and a + test for bile; the sediment was bile stained but contained no cells. The reaction for urobilinogen was 2 Ehrlich units. Examination of the blood revealed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 12,200, with 58 per cent neutrophils, 32 per cent lymphocytes, 4 per cent eosinophils, 4 per cent monocytes and 2 per cent basophils. There was slight variation in size of the red cells on smear. The sedimentation rate was 40 mm. after one hour. The prothrombin time was 15 seconds (normal, 14 seconds). The nonprotein nitrogen was 19 mg., the alkaline phosphatase 4.1 units, the bilirubin 9.8 mg. total, the cholesterol 252 mg., and the cholesterol esters 183 mg. per 100 cc. The cephalin flocculation was negative after forty-eight hours, and the thymol turbidity was 3 units per 100 cc. Blood heterophil-antibody agglutination and the blood Hinton reaction were negative. The stool urobilinogen was reduced; on at least one occasion the patient had a clay-colored stool although most of his stools were brown. The urine gave negative reactions for porphyrin and porphyrobilinogen. On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Chester M. Jones*: This is a problem of painless jaundice — its cause and what should have been done about it. I am sure I am not going to be able to say with confidence what this man had.

There was bile in the urine, and the urobilinogen may have been low; repeated urobilinogen tests on the urine during the first hospital admission would probably have given us more information about that. Aside from the elevation of bilirubin in the blood serum there were no important findings that were diagnostic. The globulin, which was really elevated, 3.7 gm., however, definitely suggests an infectious process — intrahepatic disease. The alkaline phosphatase, which was slightly above normal, would fit in with any intrahepatic disturbance. The cephalin flocculation was borderline and does not help. The thymol turbidity was also slightly above normal and would fit in better with intrahepatic disease than with extrahepatic block; it dropped with improvement in the prothrombin values and in the patient's clinical condition. The positive heterophil-antibody agglutination in the dilution of 1:320, which subsequently dropped to a much lower figure, should be taken seriously. Up to that point I should think that one had a right to consider infectious hepatitis of some sort — epidemic viral hepatitis, serum hepatitis or infectious mononucleosis with involvement of the liver. The high globulin, the atypical lymphocytes and the slight elevation of phosphatase and the thymol turbidity test are consistent with primary intrahepatic disease.

There was no story of pain at the time of admission to the other hospital — nothing to suggest gallstones or increasing extrahepatic block. There was a variation in the degree of interference with the flow of bile. The cholecystogram four weeks after admission to the other hospital revealed a nonfilling gall bladder, but I do not see how I can interpret it. This man clinically had something wrong in the liver as evidenced by severe jaundice and the bilirubin that was fairly well elevated. There was no reason, therefore, why the dye should have been excreted by the liver and should have found its way into the gall bladder in sufficient concentration to give a good x-ray picture. The fact that it did not is not sufficient evidence for me to assume that the cystic duct was blocked since it could have been due to failure of the liver to excrete the dye.

The barium-enema examination is of interest. It is reported as demonstrating chronic superficial colitis without any evidence of ulcerations. I suppose the radiologists were trying to describe edema of the mucosa without ulceration, which could go with an acute infectious process rather than so-called idiopathic ulcerative colitis. Certainly, the diagnosis of ulcerative colitis was not entertained or I should have been given other information; I am sure that sigmoidoscopic examination would have been performed. Moreover, nothing in the story seems to go with it. I am inclined, therefore, to overlook that statement.

The calcification in the region of the head of the pancreas in a young man of twenty-one, if it was not in the paravertebral lymph nodes and therefore misdiagnosed, is a very important finding. With a chronic pancreatitis progressing to calcification, there is no doubt that at times associated pancreatic edema and swelling are severe enough to cause the degree of jaundice that this patient had. He had had no pain, however, and nothing to suggest pancreatic disease. Furthermore, calcification is not a sign of new growth. These calcified areas could have been in paravertebral lymph nodes or in an aberrant common duct — a possibility I should like to remember as I go on.

At any rate the patient grew better under careful treatment in the other hospital, and the symptoms disappeared. When jaundice recurred in the absence of fever or abdominal pain, he was admitted to this hospital. At that time it was not possible to demonstrate an enlarged liver and spleen. He was deeply jaundiced, however, and had a curious dark-brown pigment. I suspect, without being able to prove it, that this pigment was due to chronic itching and scratching, and that the skin lesions were caused simply by trauma. There were no spider angiomas to go with chronic intrahepatic disease, but that does not rule it out. There was no lymphadenopathy, but

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there was tenderness in the right upper quadrant and possibly on the left. The laboratory data were of less help the second time than those reported the first time. There was something in the first set that pointed to a diagnosis of intrahepatic disease. In the second set, in spite of the degree of jaundice (the bilirubin was almost 10 mg. per 100 cc.), he had little to suggest intrahepatic disease — the cephalin flocculation was negative and the thymol turbidity, heterophil-antibody and cholesterol, both total and percentage of esters, were normal; practically, I am left with the statement that this man was jaundiced and that the jaundice was not due to obstruction because most of the stools were brown although one or two were much lighter and possibly one was clay colored.

What diagnosis is possible here? I think that on admission to the other hospital a reasonable possibility was infectious mononucleosis; at least a positive heterophil-antibody agglutination at 1:320 that subsequently dropped to a much lower figure and then finally became absolutely normal should mean that that diagnosis is tenable. The liver is practically always involved in infectious mononucleosis although jaundice is relatively uncommon. Infectious mononucleosis, which would fit in with the symptoms and the laboratory tests that were done at the first hospital admission, does not seem to explain the findings on the second admission; therefore, if the patient had had a hepatitis due either to epidemic infectious hepatitis or infectious mononucleosis, he must have had something else in the second admission, such as extrahepatic block.

What are the conditions that can produce extrahepatic block in a twenty-one-year-old patient five months after a previous attack of jaundice? He could have had gallstones, of course. He could have had persistence of enlarged diseased lymph nodes along the common duct, but there is no suggestion in the physical examination that any such process existed, and I might add that there is a dearth of x-ray evidence. Do we have the one film that showed calcification of the pancreas? I am not willing to accept that diagnosis, but I cannot disregard it. Did the physicians get the x-ray films from the other hospital and interpret them?

Dr. Joseph Hanelin: I did not see them, and we do not have them now. We made no x-ray examination at all.

Dr. Jones: In my own experience, I do not recall having seen calcification of the pancreas at this age. I have seen mistakes made in the interpretation of calcification in this area; usually calcification in paravertebral lymph nodes has been misinterpreted. I suppose it is possible that the calcification was in a calculus in the common bile duct near the ampulla. There is nothing against such a diagnosis. He had jaundice and light and dark stools; that sequence of events is perfectly consistent with a stone in the common duct. He never had pain at any time or episodes of chills and fever, and in their absence in a young person I am not too happy about that diagnosis.

Could he have had a malignant tumor involving the ampulla or the head of the pancreas? Usually, that occurs at a much later decade than the beginning of the third so I think such a diagnosis is not particularly logical. On the basis of the information given, particularly on the basis of information that is missing, I cannot make an absolute diagnosis. I shall say that this man probably had some type of hepatitis and that he also had some extrahepatic block, a stenosing cholangitis, some inflammatory process in the bile duct or possibly gallstones to explain the rest of the story. He may have had a hepatitis that continued to the final admission.

I think the important thing, because after all this exercise is to teach us on the basis of our own and other people's mistakes, is that a decision was made to find out why this man had recurrent attacks of jaundice with no other findings. That decision was correct. An exploration should have been done so that if there was any correctable cause of jaundice it could have been taken care of at that particular moment, and that was apparently done.

Dr. Daniel S. Ellis: Would you have recommended a liver biopsy before exploration?

Dr. Jones: Yes.

Dr. Benjamin Castleman: A liver biopsy was the operation.

Dr. Farahe Maloof: Do you think the pigment could have been caused by something more than itching?

Dr. Jones: It may have been from more than the itching; increasing pigmentation of the skin is seen with intrahepatic or extrahepatic obstruction of any degree, but it is most marked where scratching occurs. On the other hand it appears without any itching at all, and the skin presents a curious dirty-brown color, as if it were washed in places and not in others. It suggests the possibility of chronic intrahepatic disease. The second part of the story bothered me a great deal; he may have had an infectious hepatitis that had gone into a chronic phase.

Dr. Ellis: You do not really believe that, because you have just pointed out that with hepatitis going into a chronic stage and this much jaundice, the liver-function tests would certainly have been different.

Dr. Jones: I believe that hepatic infection was the cause of the first admission. Certainly, when there was so much jaundice the second time, with no more findings of intrahepatic disease and no palpable liver or spleen, it is difficult to maintain that infectious mononucleosis was the condition for which the exploratory operation was performed.

Dr. Castleman: You think he had infectious mononucleosis and another disease?

DR. JONES: I think he had infectious mononucleosis; I do not know how to interpret that laboratory finding otherwise. If somebody will say a dilution of 1:320 means nothing, I shall be willing to drop that. Any case of infectious mononucleosis is likely to involve the liver to some extent. I do not believe it would explain the final picture.

DR. CASTLEMAN: Dr. Kranes, do you believe this could explain the second admission?

DR. ALFRED KRANES: This patient had an attack of acute infectious hepatitis from which he recovered, and then he had a relapse. I had not realized how sick he was. Ten to 15 per cent of all people who have infectious hepatitis may recover without developing a positive cephalin flocculation.

DR. JONES: But, with relapse, the percentages would be much lower, and one would expect to feel the liver or the spleen or both on palpation. Then there was this very curious set of negative findings and not a single positive test except the hyperbilirubinemia.

DR. CASTLEMAN: You would agree with Dr. Jones, then, that if you did not have the story of the first admission, you would think more of extrahepatic disease than infectious hepatitis?

DR. KRANES: All we have is a patient with jaundice; there was no clue to whether it was due to intrinsic liver disease or obstruction; neither were tests positive. He did not have a high phosphatase, a high cholesterol and so on.

DR. ELLIS: He had a low urinary urobilinogen. If he had a great deal of disease in the liver because of infectious hepatitis, one would expect the urine urobilinogen to have been much higher.

DR. CASTLEMAN: I notice from the record that Dr. Ellis thought, before he put the exploring needle into the liver, that the patient probably had a cholangiolitic cirrhosis, apparently developing from infectious hepatitis. Is that correct?

DR. ELLIS: I thought that he had had the same disease all along because the only parenchymal liver disease that I know of that might produce this picture with the jaundice of the degree that he had, at the end of a year and a half, is an intrahepatic cholangiolitic biliary type of cirrhosis. We have seen it in some of those cases with deep jaundice and relatively little impairment of liver function over a long period.

CLINICAL DIAGNOSIS

Cholangiolitic biliary cirrhosis.

DR. CHESTER M. JONES'S DIAGNOSES

Infectious mononucleosis, recovered.
Extrahepatic obstruction.

ANATOMICAL DIAGNOSES

Sclerosing cholangitis involving hepatic, cystic and common bile ducts.
Bile stasis, with biliary cirrhosis, early.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Biopsy showed severe bile stasis characteristic of extrahepatic obstruction; for that reason operation was performed. Dr. Mixter, will you tell us about the operation?

DR. CHARLES G. MIXTER, JR.: When we operated on this patient we believed that the most likely diagnosis was a stone but we were not too happy about that diagnosis. At the time of the operation the striking features were large, succulent lymph nodes around the foramen of Winslow and the common duct, a normal gall bladder without stones and a greatly enlarged and thickened common duct with a very narrow lumen. A cholangiogram at operation showed a tiny trickle of dye going through the common duct and up into the hepatic ducts.

DR. HANELIN: The cholangiogram, unfortunately, is not too good, but it does show the common duct faintly outlined; its lower third particularly is markedly decreased in caliber, its lumen being considerably narrowed. The duct above the lower third is also narrowed somewhat. Some of the biliary radicles are rather small, and some seem to be overdistended.

DR. MIXTER: We could only insert a 1-mm. probe through the lumen of the distal common duct. We put a T tube into the common duct; I am not sure that was the correct procedure because we had to force the T tube down through into the ampulla of Vater. The patient did well for a few days and then became extremely sick, and a temperature of 107.5°F. developed. We re-explored him in the hope that we might find a subhepatic collection of pus, but we could not and he died the next day.

DR. JONES: This type of interference with the flow of bile secondary to narrowing of the bile ducts is the condition that does cause itching and pigmentation.

DR. CASTLEMAN: The immediate cause of death was a hemorrhagic pancreatitis, with extensive fat necrosis. There was a sclerosing, stenosing cholangitis of the common duct that extended into both hepatic ducts. This unusual condition is called idiopathic because here we have no indication at all of its cause. Unfortunately, the T tube probably compressed the pancreatic duct sufficiently to produce the obstruction and the final pancreatitis. The pancreatic and common bile ducts met in the papilla. I doubt whether very much could have been done for this patient because the sclerosis extended quite high up into the hepatic ducts and even into the smaller intrahepatic radicles, which were not dilated.

At autopsy there was a good deal of central necrosis in the liver, all of which had occurred postoperatively, so that it was hard to be sure what was in the liver originally; however, the aspiration liver biopsy did not give evidence of hepatitis. Of course, it may have been present in the past, but I am inclined to believe that both admissions were for the same condition — the sclerosing, stenosing cholan-

gitis. This had produced almost a pin-point lumen, and on microscopical examination the mucosa and submucosa were replaced by fibrous connective tissue; the whole wall was thickened, suggesting that the disease had been present for a long time. We do not know how long but certainly not from birth; patients with the congenital type of bile-duct stenosis die in infancy.

DR. JONES: I should like to ask Dr. Kane if he thinks the evidence presented in the protocol warrants a diagnosis of infectious mononucleosis. There was a high titer for a period, a moderate leukocytosis and abnormal monocytic cells that subsequently disappeared.

DR. LEWIS W. KANE: Yes, I do. As a matter of fact he was my patient; we seriously considered that diagnosis at first and treated him with it in mind. However, occasional cases of infectious hepatitis of viral origin that are not believed to be infectious mononucleosis may have a positive heterophil-antibody agglutination so that we cannot be certain. As time went on, it became apparent that he had some form of obstructive jaundice. I thought he had a common-duct stone, but I was not happy with that diagnosis. Exploration was the next logical step.

DR. MIXTER: When this case was discussed at medical rounds at the other hospital during the first admission, the physicians' conclusion and the discharge diagnosis were infectious mononucleosis.

DR. JONES: The most striking finding in the laboratory data on the first admission was the high globulin, which is not found with intrahepatic block to the flow of bile; it indicates temporary disturbance of hepatic function and is the sort of finding seen in infectious mononucleosis.

DR. CASTLEMAN: Of course, we cannot rule that out.

DR. MIXTER: Mention might be made about the procedure of putting the T tube through the ampulla, which is quite widespread throughout the country at present. We have recently had a number of cases in the hospital that tend to make us believe that that procedure may not be entirely harmless — that it may give rise to pancreatitis.

CASE 40042

PRESENTATION OF CASE

First admission. A fifty-three-year-old housewife, gravida II, para II, was admitted to the hospital because of pain in the left costovertebral angle.

Six days previously the patient awoke with a pain in the left costovertebral angle and lower part of the chest. The pain was severe and steady and did not radiate; it was not affected by respiration but was associated with nausea and vomiting. The stools after saline cathartics had been taken were loose and watery. Only once was there an episode of dysuria, when the patient noticed burning on urination.

On examination, the heart was slightly enlarged, with systolic murmurs at the apex and base. The abdomen was tense and distended, and there was a palpable mass on the left side. There was definite tenderness in the left upper quadrant and left flank, as well as bilateral costovertebral-angle tenderness. Examination of the rectum was negative.

The temperature was 100°F., the pulse rate 80, and the respirations 20. The blood pressure was 170 systolic, 90 diastolic.

The urine had a specific gravity of 1.010 and gave a trace test for albumin; the sediment was loaded with white cells. The urine culture grew out *Escherichia coli.* Examination of the blood revealed a hemoglobin of 80 per cent (Sahli) and a white-cell

FIGURE 1.

count of 18,200, with 85 per cent neutrophils. The nonprotein nitrogen was 26 mg. per 100 cc. A roentgenogram of the chest showed only evidence of old tuberculosis. On an intravenous pyelogram there was good excretion bilaterally. A retrograde pyelogram demonstrated a mass 8 cm. in diameter rotating the left kidney clockwise. The mass extended far laterally, and distorted one of the upper calyxes on the left.

On the nineteenth hospital day, a left nephrectomy was performed. A polycystic kidney, with a perinephric abscess, was found (Fig. 1). Postoperatively, the patient did well and was discharged after three weeks.

At the time of a follow-up visit three weeks later the blood pressure was recorded as 185 systolic, 115 diastolic; a culture of the urine was negative.

During the next four months she visited the clinic and was free of symptoms. Another intravenous pyelogram taken at the end of that time showed what appeared to be a normal-sized right kidney in which there was prompt excretion of poorly concentrated dye.

Final admission (thirteen years later). The patient had been well and had not been seen again until three months before admission, when she entered the clinic complaining of pain in the right flank of two weeks' duration. She had not had any urinary symptoms. On physical examination she was thin but in no acute distress. A large, nontender mass was palpable in the right side of the abdomen. The blood pressure was 160 systolic, 90 diastolic. The urine had a specific gravity of 1.008 and was negative for albumin; the sediment contained many white cells. A urine culture gave an abundant growth of *Proteus vulgaris*. The nonprotein nitrogen was 50 mg. per 100 cc. Later, an intravenous pyelogram failed to demonstrate the right kidney. She was treated with Thiosulfyl; however, her condition did not improve. On a subsequent visit the hemoglobin was found to be 7.7 gm. per 100 cc., and she was admitted to the Overnight Ward, where she was given two transfusions. About a week later she returned because of anuria. Examination at this time showed an enlarged heart with the apex at the anterior axillary line, an aortic second sound louder than the pulmonic and Grade 2 systolic murmurs at the apex and base, but no distention of the neck veins. A large, slightly tender mass filled almost the whole right side of the abdomen. The retina showed + vascular changes.

The temperature was 100°F., the pulse 90, and the respirations 20. The blood pressure was 145 systolic, 85 diastolic.

The urine was light yellow, had a specific gravity of 1.002, and gave a trace test for albumin; the sediment contained many white cells and bacteria. Examination of the blood revealed a hemoglobin of 11 gm. per 100 cc. and a white-cell count of 22,000, with 79 per cent neutrophils. The serum nonprotein nitrogen was 88 gm., the calcium 9.1 mg., the phosphorus 5.0 mg., and the total protein 6.2 gm. per 100 cc., with an albumin-globulin ratio of 1.8; the sodium was 130 milliequiv., the chloride 92 milliequiv., the potassium 6.2 milliequiv., and the carbon dioxide 15 milliequiv. per liter. A pyelogram demonstrated a large right kidney with a ureter in which the course was normal. A catheter could not be passed beyond the level of the third lumbar vertebra.

Eighteen hours after admission an operation was performed.

Differential Diagnosis

Dr. Alexander Leaf*: It seems certain, from Figure 1 and the pathological diagnosis, that the left kidney, which was removed, was involved in polycystic disease. The removal of one polycystic kidney at a time when the opposite kidney seemed to be normal at least by x-ray examination raises the possibility that the patient had unilateral polycystic kidney disease that was cured by the operative procedure, and that the difficulty thirteen years later was due to some unrelated involvement of the remaining kidney. There is disagreement about whether renal polycystic disease occurs as a unilateral lesion. Most authorities apparently believe that it can occur as a unilateral lesion and cite an incidence of unilateral involvement of about 8 per cent of patients with polycystic kidney disease. Cases such as this, however, make the interpretation of what is unilateral cystic disease of the kidney difficult. In this case a thirteen-year period intervened before the disease became manifest in the remaining right kidney; the condition of the right kidney might easily have been misinterpreted thirteen years earlier and the patient considered to have had unilateral polycystic disease. Such intervals between manifestations of the polycystic disease in one kidney and then in the other have been reported in the literature although they are unusual. It is my belief that the patient had bilateral polycystic kidney disease and that the final admission was for complications affecting the remaining polycystic kidney.

Dr. Castleman mentioned at a previous clinicopathological conference the interesting and mystifying clinical observation that the manifestations of polycystic kidney disease appeared largely at two periods in the life span of persons — namely, in infancy and at middle age — and did not often occur between infancy and the fourth decade of life. The recent work of Lambert,[1] which Dr. Castleman mentioned, gives some explanation of this situation. Lambert showed by reconstructing the nephrons of the polycystic kidneys in infants that the cysts that are formed do not connect with the pelvis; therefore, there is actual obstruction to all outflow of urine, and the infant succumbs very early to the lesion. On the other hand in the adult there are two types of cyst: a glomerular cyst, which is similar to that in the infant, does not connect with the pelvis; the other, a cyst of the tubular type, does connect with the pelvis. Lambert was able to show by renal-function studies that these cystic tubules actually excrete and reabsorb water, excrete urea and so forth. Probably, the continued function in these cystic tubules is the reason that the disease has such a protracted course

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in the adult even after early evidence of renal insufficiency develops.

To return to our present problem I must decide the cause of the acute obstructive episode that affected the patient's remaining kidney. May we see the x-ray films?

DR. STANLEY M. WYMAN: The film of the chest is not unusual except for the findings to be expected in hypertensive heart disease — prominence of the left ventricle and slight aortic tortuosity. There are minimal old scars, perhaps from tuberculosis. The right-kidney shadow seems to be a great deal larger than normal, and its lower portion in particular shows a rounded protuberance. Lying within that protuberance are a number of small calcifications. The right kidney functioned slightly on the intravenous examination. A small amount of contrast material is in an upper calyx, which is seen on these two views. Films from the retrograde examination show the kidney catheter passing up to the upper portion of the ureter but failing to go beyond this point. There is no clue on these films, as far as I can see, to why the catheter did not go any farther, and the lesion is not outlined.

DR. LEAF: Do you see any evidence in the shadow of the liver of cystic disease involving the liver? Bell[2] reports that about 30 of his 70 patients had liver involvement.

DR. WYMAN: We would not see the cysts per se unless they were protruding into the air-filled lung. That does not appear on these films. The liver is quite smooth and is not enlarged; therefore, I do not see anything to suggest cysts in the liver.

DR. LEAF: There are several possible causes for the anuria that developed. How complete the anuria was is difficult to judge from the clinical record; in one paragraph anuria was mentioned, and in the next the urinalysis was reported so something must have been excreted. The patient received two blood transfusions — the only statement in the history that suggests acute renal insufficiency of the "lower-nephron-nephrosis" type. However, these were given two weeks before admission. Certainly, some evidence of lower-nephron nephrosis should have preceded the onset of anuria occurring after that interval; therefore, I do not think the blood transfusions had anything to do with the obstruction or anuria. She also received a sulfonamide. For those who, like myself, have not heard what Thiosulfyl is, it is sulfa-methyl-thio-diazole, which has been recommended for the treatment of urinary-tract infection and is alleged to have a very low toxicity. On that basis and in the absence of any crystals in the urine, I shall discard the possibility of obstruction from a sulfonamide.

Characteristically, about a third of the patients with polycystic kidney disease have intermittent episodes of hematuria. Apparently, when the cysts enlarge they may break small vessels in their walls, causing bleeding into the cyst. The cysts may then rupture into the pelvis and extrude their contents. It is possible that the passage of a blood clot in the patient under discussion resulted in obstruction that did not show up in the x-ray films. I think, however, there would have been some evidence of hematuria; yet no blood at all was found in the urine.

A huge kidney may conceivably have been producing mechanical obstruction of the ureter either by compressing it or by kinking it, but I have not heard of this so I shall discard that possibility.

Finally, there was evidence of calculi in the kidney. The patient was known to have had an infected kidney with pyelonephritis as evidenced by fever, the elevated white-cell count, the positive urine culture and many bacteria and white cells in the sediment. That, with the evidence that calculi were present in the kidney, makes me suspect that obstruction from a small ureteral calculus had occurred even though no stone was seen at the tip of the catheter. There is a possibility about which I shall have to ask Dr. Castleman. Could these small calcifications noted in the x-ray films have been in the cysts of the kidney? I could not find any description of calcification in blood-filled cysts, but it would be surprising if they did not have calcification.

DR. BENJAMIN CASTLEMAN: I believe that can occur.

DR. LEAF: It is possible that what we are interpreting as stones was calcification in the cysts. Although the patient may have been cured of the polycystic disease by removal of one kidney thirteen years earlier and the final episode may have represented a huge hydronephrotic kidney or some other disturbance in the kidney, my diagnosis is polycystic kidney disease affecting the remaining kidney, with pyelonephritis, renal calculi and renal insufficiency. The episode of oliguria, for which she was operated on, I should attribute to obstruction by a calculus. I believe that a patient with obstruction should be operated on to relieve the obstruction, the cause of which would most certainly become apparent at operation.

DR. CASTLEMAN: Dr. Colby, have you any comment?

DR. FLETCHER S. COLBY: It is not clear to me why a nephrectomy was done thirteen years before the final admission. Was it because of the cysts or because of infection?

DR. CASTLEMAN: Because of the abscess.

DR. COLBY: That is not an indication for the removal of the kidney unless the perinephritic abscess was secondary to an infected cyst. Certainly, in the presence of polycystic disease, one would hesitate to remove the kidney unless infection was present all through the cysts. I should like to ask Dr. Castleman if in his experience here in this hospital he has ever come across a patient with unilateral polycystic disease of the kidneys?

DR. CASTLEMAN: I do not believe we have had a case here.

DR. COLBY: I suspect that, since polycystic disease is a congenital condition, the patients who have been described as having unilateral polycystic disease merely had multiple simple cysts of one kidney. My experience and that of most others is that real polycystic disease is always a bilateral condition.

CLINICAL DIAGNOSIS

Polycystic kidney, with obstruction.

DR. ALEXANDER LEAF'S DIAGNOSIS

Polycystic kidney disease, bilateral.

ANATOMICAL DIAGNOSIS

Polycystic kidney disease, bilateral, with thirteen-year survival after nephrectomy.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation the surgeon found a fibrin plug in the upper end of the ureter that had apparently blocked it. He performed a nephrostomy and drained the polycystic kidney quite well, but the kidney was severely infected. The patient died two weeks after operation.

At autopsy we found, in addition to a severely infected kidney, an extensive bronchopneumonia. She had a large hemorrhagic infarct of the right side of the brain, which I am sure must have had a great deal to do with her death. The liver contained multiple cysts, the largest measuring 3 cm. in diameter.

DR. LEAF: How much disease do you think the right kidney would have shown if the patient had succumbed at the time of the first operation?

DR. CASTLEMAN: I think it would have looked just like the other.

DR. COLBY: The disease can be more advanced in one kidney than the other. The pyelograms may not have demonstrated anything on the right side thirteen years before death in either the outline or the calyceal system.

DR. WYMAN: We do not have that pyelogram, which might have shown something in retrospect.

DR. CASTLEMAN: The retrograde pyelogram was done on only one side.

DR. LEAF: The intravenous pyelogram from her earlier admission was reported.

DR. CASTLEMAN: Yes; the intravenous pyelogram revealed a suggestion of a soft-tissue mass on the right side of the abdomen. I believe that at the time of the original operation the surgeons thought that there was only an abscess involving the kidney and did not recognize the polycystic kidney on the operating table.

REFERENCES

1. Lambert, P. P. Polycystic disease of kidney: review. *Arch. Path.* 44: 34-58, 1947.
2. Bell, E. T. *Renal Disease.* Second edition. 448 pp. Philadelphia: Lea & Febiger, 1950. P. 109.

ANNOUNCEMENT FOR GROUPS USING CASE RECORDS

The Massachusetts General Hospital wishes to announce that it has obtained a grant from the United States Public Health Service to supply pertinent 35-mm. lantern slides of x-ray films, gross photographs and photomicrographs to go along with the current Case Records to groups who use these exercises for teaching purposes.

It is planned to supply about 5 lantern slides with each issue of the *Journal* (2 cases) — that is, approximately 250 slides per year (these may be added to the teaching files of the group). The grant included the following conditions:

> **"The project will be limited to 100 groups. The leader of each group should fill out an application stating the character and size of the group, how often it meets, and its methods of presentation of the Case Records. It is proposed that in order to limit the number of groups and to safeguard selection, each group pay a yearly stipend of $25.00. (The actual cost will be about $100.00.)"**

Applications for this service may be obtained from Dr. Benjamin Castleman, Massachusetts General Hospital, Boston 14, Massachusetts.

The New England
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MICE AND MEN

THAT there is some association between cigarette smoking and cancer of the lung is generally accepted in the medical profession. Statistical evidence of this correlation has been accumulating over a number of years and is rapidly becoming public knowledge, to the extent that the tobacco interests have found in it some cause for alarm.

This is demonstrated by a recent full-page advertisement of the Tobacco Industry Research Committee, headed, unfortunately, "A Frank Statement to Cigarette Smokers." For the statement is not quite frank, opening as it does with the assertion that "Recent reports on experiments with mice have given wide publicity to a theory that cigarette smoking is in some way linked with lung cancer in human beings."

This opening is regrettable in that the real case against cigarette smoke is based not on experimental evidence derived from mice but on statistical material gathered from men. As stated in an editorial on the same subject published in these columns only a week ago, "It must be stressed that the animal experiments were undertaken because of the human evidence already at hand."

Any correlation between the results of experiments on mice and those of observations on human beings is beside the point, however. The real point is that a matter of such universal concern should have all possible light shed on it, from all possible angles. This is in the interest of humanity and, in the long run, of the tobacco industry, and is recognized as such by many of their number. These are the ones who are willing to face squarely the facts that cancer of the lung has increased more in the last twenty years than any other form of neoplastic disease; that the increase is largely among males, who are still by far the greatest users of tobacco, and that a projection of the present increase in death rates from cancer of the lung will put it ahead of all other forms of the disease within the next ten years.

To the end that all possible information may be gathered as rapidly as possible, the Cancer Research Institute of the New England Deaconess Hospital, in co-operation with the Committee on Cancer of the Massachusetts Medical Society, is asking the help of the fellows of the Society. This request, which has been or will soon be received by each member, is in the form of a letter and a confidential questionnaire relating to the personal habits of the physician so far as tobacco is concerned.

Physicians are known to be among the most faithful customers of the cigarette manufacturers. Any change in their habits regarding the use of tobacco, and the reasons for it, will be of interest and of value in the study of these immense problems. It is hoped that all who are really interested will comply with the request.

THIRD INTERNATIONAL CONGRESS OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

EVEN more successful than previous gatherings was the Third International Congress of Electroencephalography and Clinical Neurophysiology, held August 17-22, 1953, at Radcliffe College in Cambridge. The number of delegates registered was twice as great as that at the second meeting four years previously. And in spite of difficulties in foreign exchange 34 countries were represented, the delegates from far afield being rewarded by an outstanding program presented by speakers from France, Italy, Belgium, Germany, Holland, Switzerland, England, Spain, Denmark, Australia, Japan and Peru, as well as from the United States and Canada.

Not the least important feature of this gathering was the fact that the foreign delegates were so well housed and cared for — an achievement of no small proportions on the part of the sponsors and officers of the congress. It is thus that international relations, in a time of weakened ties abroad, are strengthened. The International Federation of Societies for Electroencephalography and Clinical Neurophysiology and affiliated organizations at this session earned the thanks not only of persons interested in the special fields represented but also of those who recognize the value of scientific and cultural gatherings in this country and abroad.

OPERA SPECIALIA

ELSEWHERE in this issue of the *Journal* a modest innovation is made with the publication of the first of a series of "special articles" — a series that, it is hoped, will stretch out into the vast future with no temporal end in sight. The series is opened at this critical moment with an informative paper on income-tax problems by a legal authority on the subject. In this communication, adapted from a chapter in a book of information useful to physicians, soon to be published by Little, Brown and Company, Mr. Gitlin essays to instruct the physician in the art of being fair to himself and his family without evading his federal responsibilities.

The proposed special articles, to be published at irregular intervals, are intended to include a variety of topics that may not ordinarily be considered as falling properly into the categories either of original scientific and clinical papers or of medical progress. This is not a promise, however, for on the other hand they may occasionally be clinical or scientific in nature, although with a flavor that renders them in some way distinctive. Their purpose is to give greater flexibility to the content of the *Journal*, adding to its general interest and usefulness as much, and to its incidental confusion as little, as possible.

It is proposed to publish in the 1954 series additional chapters — Mr. Gitlin's being a first sample — from *The Physician, His Practice and His Business*, as well as articles on social, economic and health problems as they occur in various lands.

HUMANE CARE OF LABORATORY ANIMALS

Too often, the least temperate elements of society embarrass and hinder medical research by shrill and exaggerated denunciation of those who perform vital experiments with laboratory animals. The fourth annual meeting of the Animal Care Panel, recently held in Chicago, is therefore a welcome reminder that the group most concerned — professional workers in laboratories — are making every effort to ensure the comfort and best care of the helpless subjects of necessary and valuable experiments. The organization was created by a few professional workers in charge of animals and their quarters as a medium for the exchange of ideas regarding standards of housing, nutrition and sanitation; proceedings of each session are published, and members of the Panel are available for consultation on problems encountered in the care of laboratory animals.

The agenda of the latest meeting included reports on nutrition in laboratory dogs and small animals and on the conduct of animal experimentation in Great Britain, where licensing legislation similar to that vociferously advocated by certain groups in the United States has long been in effect. In addition the executive secretary of the newly formed Institute of Animal Resources discussed the program of the Institute and the development of the concept of controlled pure strains of animals.

Physicians should be the first to appreciate the value of the Panel, not only for its interesting and productive meetings but also for the mere fact of its existence. It is to be hoped that the Panel and its activities will be sufficiently publicized to become familiar to the group for whose benefit all scientific experiments are performed — the public itself.

In the efforts to get rid of quacks, by an act of the Legislature of one of our distant States, the rumor is that the character of the reformatory process is calculated to multiply them rapidly.

Boston M. & S. J. *February 1, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CAPONE — Angelo J. Capone, M.D., of Somerville, died on January 14. He was in his forty-seventh year.

Dr. Capone received his degree from Tufts College Medical School in 1931. He was on the staffs of the New England Sanitarium and Hospital, Somerville, Symmes Arlington and Winthrop Community hospitals. He was a fellow of the American Medical Association and the American College of Surgeons.

He is survived by his widow and a daughter.

D'ERRICO — Emilio D'Errico, M.D., of Winchester, died on January 7. He was in his sixtieth year.

Dr. D'Errico received his degree from Tufts College Medical School in 1923 and later was a member of the faculty. He was chief of obstetrics, Lawrence Memorial Hospital, Medford, and senior visiting physician in obstetrics, Boston City Hospital. He was a fellow of the American College of Surgeons, the American Academy of Obstetrics and Gynecology and the American Medical Association and a member of the New England Obstetrical and Gynecological Society.

He is survived by his widow, two sons and two daughters.

LOUGEE — William W. Lougee, M.D., of Malden, died on January 10. He was in his eighty-seventh year.

Dr. Lougee received his degree from New York University Medical College in 1898. He was formerly a member of the staff of the Malden Hospital and medical inspector of the Malden schools.

He is survived by his widow and two sons.

O'CONNOR — Alfred S. O'Connor, M.D., of Worcester, died on January 15. He was in his sixty-second year.

Dr. O'Connor received his degree from Tufts College Medical School in 1918. He was chief of pediatrics at the Worcester City Hospital, formerly assistant professor of clinical pediatrics, University of Vermont College of Medicine and a member of the staffs of the Worcester Hahnemann, Belmont, Marlboro and Southbridge hospitals. He was a member of the New England Pediatric Society and a fellow of the American Medical Association and the American Academy of Pediatrics.

He is survived by his widow and two sisters.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1953

RÉSUMÉ

DISEASE	DECEMBER 1953	DECEMBER 1952	SEVEN-YEAR MEDIAN
Chancroid	3	1	1
Chicken pox	1184	3201	1455
Diphtheria	3	2	18
Dog bite	736	725	648
Dysentery, bacillary	42	7	4
Encephalitis, infectious	0	1	2
German measles	77	103	67
Gonorrhea	192	149	186
Granuloma inguinale	0	0	0
Hepatitis, infectious	117	144	81†
Lymphogranuloma venereum	0	1	1
Malaria	0	1	1
Measles	49	81	459
Meningitis, meningococcal	6	9	8
Meningitis, Pfeiffer bacillus	1	4	8
Meningitis, pneumococcal	3	3	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	7	5	4
Mumps	1288	773	847
Poliomyelitis	53	24	17
Salmonellosis	14	29	4
Scarlet fever	371*	431	431
Syphilis	198	104	180
Trichinosis	0	2	3
Tuberculosis, pulmonary	195	155	207
Tuberculosis, other forms	6	9	12
Typhoid fever	0	1	1
Undulant fever	0	2	2
Whooping cough	157	150	363

*Includes streptococcal sore throat.

†Four-year median.

COMMENT

Diseases below the seven-year median included chicken pox, diphtheria, measles, scarlet fever and whooping cough.

The 49 cases of measles reported make this by far the lowest figure for the month of December in the history of the State. This is the fifteenth consecutive month that a new low record has been established since 1906.

Three cases of diphtheria were reported in December, continuing a level that has been more or less constant for the past seven months, in contrast to previous seasonal fluctuations.

With one exception (1952) the figure of 157 reported cases of whooping cough was the lowest for the month of December since 1915.

Diseases above the seven-year median were bacillary dysentery, infectious hepatitis, mumps, poliomyelitis and salmonellosis.

Although the 42 reported cases of bacillary dysentery represented a high incidence for December this was a decline from the preceding month — a trend that has been evident since the early fall.

Poliomyelitis continued at a high level, the number of cases reported (53) being the highest since 1927.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Anthrax: Boston, 1.

Diphtheria: Ayer, 1; Fall River, 1; Southbridge, 1; total, 3.

Dysentery, amebic: Wrentham, 5.

Dysentery, bacillary: Boston, 13; Billerica, 1; Brookline, 1; Cambridge, 4; Chelsea, 2; Everett, 1; Fitchburg, 8; Greenfield, 2; Medford, 1; Saugus, 1; Springfield, 1; Waltham, 1; Watertown, 2; Worcester, 3; Wrentham, 1; total, 42.

Hepatitis, infectious: Alford, 1; Arlington, 1; Belchertown, 1; Boston, 22; Brockton, 4; Brookline, 1; Cambridge, 11; Chelsea, 8; Fairhaven, 1; Falmouth, 1; Fort Devens, 1; Greenfield, 1; Hingham, 1; Lowell, 1; Lynn, 8; Medford, 1; Milford, 1; New Bedford, 2; Newton, 1; Northboro, 1; North Brookfield, 10; Oxford, 1; Paxton, 1; Plymouth, 3; Salem, 1; Scituate, 1; Shrewsbury, 1; Southboro, 1; Springfield, 5; Upton, 1; Watertown, 3; Webster, 4; Wellesley, 1; Westboro, 1; Westport, 1; Worcester, 13; total, 117.

Meningitis, meningococcal: Arlington, 1; Boston, 1; Fall River, 1; Springfield, 1; Wilmington, 1; Worcester, 1; total, 6.

Meningitis, Pfeiffer bacillus: Medway, 1.

Meningitis, pneumococcal: Cambridge, 1; Peabody, 1; Pittsfield, 1; total, 3.

Meningitis, undetermined: Arlington, 1; Fall River, 1; Haverhill, 1; Lawrence, 1; Leicester, 1; North Brookfield, 1; Somerville, 1; total, 7.

Poliomyelitis: Amherst, 1; Athol, 2; Attleboro, 2; Bedford, 1; Boston, 2; Concord, 1; Dedham, 1; Easton, 1; Everett, 1; Falmouth, 1; Fort Banks, 1; Hadley, 1; Haverhill, 1; Lynn, 2; Marshfield, 2; Melrose, 1; Middleboro, 1; Milford, 1; Newton, 3; Northampton, 2; Orange, 7; Oxford, 1; Pittsfield, 1; Quincy, 2; Reading, 1; Rockland, 1; Rowley, 1; Scituate, 2; Springfield, 2; Wakefield, 1; Weymouth, 1; Wilbraham, 3; Worcester, 2; total, 53.

Salmonellosis: Arlington, 1; Brockton, 1; Danvers, 2; Fall River, 1; Newton, 1; Norwood, 1; Rockland, 1; Somerville, 1; Springfield, 1; Townsend, 1; Waltham, 1; Winchester, 2; total, 14.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN FOR MASSACHUSETTS

The February schedule of the Consultation Clinics for Crippled Children in Massachusetts is as follows:

Orthopedic Clinic	Date	Clinic Consultant
Salem	February 1	Paul W. Hugenberger, M.D.
Gardner	February 2	Carter R. Rowe, M.D.
Haverhill	February 3	William T. Green, M.D.
Greenfield	February 4	Charles L. Sturdevant, M.D.
Lowell	February 5	Albert H. Brewster, M.D.
Lynn*	February 8	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Brockton	February 11	George W. Van Gorder, M.D.
Fall River	February 15	David S. Grice, M.D.
Springfield	February 16	James D. Fisher, M.D.
Pittsfield	February 17	Edward J. Coughlin, Jr., M.D.
Worcester	February 19	John W. O'Meara, M.D.
Hyannis	February 25	Paul L. Norton, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	February 2, 9, 16, 23
Fitchburg	February 3, 10, 17, 24

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

BOOK REVIEW

Gout and Gouty Arthritis. By John H. Talbott, M.D. 8°, cloth, 92 pp., with 32 illustrations. New York: Grune and Stratton, 1953. $4.00. (*Modern Medical Monographs*, No. 7.)

Dr. Talbott having been one of the leading students of this disease for the past twenty years, is especially well qualified to write this monograph on gout. He defines gout as a metabolic dyscrasia associated with an increased concentration of uric acid in the blood and body fluids. Gouty arthritis, on the other hand, refers to the articular manifestations, acute or chronic, resulting from the metabolic abnormality. The natural history of the disease in all its manifestations is well described. There are numerous prints of x-ray changes in and about joints, but unfortunately no photographs of joints in acute or chronic gout.

The modern concept of uric acid metabolism is clearly outlined. In man uric acid is the end product of purine metabolism, whereas urea is the end product of nitrogenous substances of amino acid and pyrimidin origin. In some species, such as birds and reptiles, uric acid is the end product of all nitrogenous substances, whether of purine or amino acid origin. Studies with isotopically labeled glycine indicate that gouty subjects not only are incapable of synthesizing purines (as normal persons do) but also metabolize some of the glycine directly to uric acid rather than to urea. This ability to produce uric acid from simple protein substances such as glycine is thought to be the main metabolic defect in gout.

Another advance in which Dr. Talbott and his group have been interested is the measurement of the so-called "miscible pool" of uric acid in normal and gouty subjects. This is done by the intravenous injection of a known quantity of isotopically labeled uric acid. Then comparison of the isotope concentrations in the injected uric acid and in that present in the body at the moment of mixing permits calculation of the quantity ("miscible pool") of uric acid present in the body in a condition capable of prompt mixing with injected uric acid. The "miscible pool" of uric acid in normal subjects has been found to be about 1000 mg. In gouty subjects this "miscible pool" of uric acid is always increased and may be as high as 3000 mg. or more. This large quantity is thought to be primarily due to the overproduction of uric acid from defective protein metabolism and not from any primary renal defect or impairment of uric acid excretion. Though the kidneys are frequently damaged late in the natural course of gout, they are normal in the early stages. Uric acid is thought to be completely filtered at the glomerulus and then partially reabsorbed from the collecting tubules.

Dr. Talbott and others have found that it is impractical, if not impossible, to alter significantly the "miscible pool" of uric acid in gouty subjects by dietary means alone. However, it has been found possible to increase renal excretion by various drugs, the most practical of which is Benemid, a benzoic acid compound that partially blocks the reabsorption of uric acid by the renal tubules. This substance, which is effective in doses of 1 or 2 gm. a day administered in divided doses of 0.5 gm. each, permits the renal excretion of uric acid to be increased 30 to 50 per cent in both normal and gouty subjects; it also reduces the serum uric acid level and eventually decreases the number of acute attacks of gout, and is apparently nontoxic.

Also discussed are the newer antiphlogistic substances, ACTH, cortisone and Butazolidin (phenyl butazone), all of which have a potent effect in gouty arthritis, besides having uricosuric properties. Butazolidin, which has been found remarkably effective in terminating acute gouty arthritis, has such potential toxic reactions that Colchicine remains the drug of choice.

This book is highly recommended to all practitioners of medicine as a brief and concise treatise on the diagnosis, natural history, pathological physiology and modern treatment of gout.

Victor G. Balboni, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Text-Book of Pathology: An introduction to medicine. By William Boyd, M.D., Dipl. Psych., M.R.C.P.(Edin.), F.R.C.P.(Lond.), F.R.C.S.(C), LL.D. (Sask.), D.Sc.(Man.), M.D. (Oslo), F.R.S.(C), professor of pathology, University of British Columbia, Vancouver. Sixth edition. 8°, cloth, 1024 pp., with 570 illustrations and 32 plates. Philadelphia: Lea and Febiger, 1953. $12.50.

This standard textbook, first published in 1932, has gone through 6 editions and 21 reprintings to date, and has been translated into Portuguese and Spanish. The previous edition was issued in 1947, and this new edition has been revised and amplified. The new material includes too much information to be described in this brief note. There is a good index, and the publishing is excellent. The book is recommended for all medical libraries and pathologists.

Experimental Studies in Psychiatric Art. By E. Cunningham Dax, M.B., B.S., D.P.M. with a foreword by Sir Steuart Wilson. 8°, cloth, 100 pp., with 51 plates. Philadelphia: J. B. Lippincott Company, 1953. $5.00.

This monograph deals with a study of painting and music in connection with mentally disturbed persons. A list of references is appended to the text, which is well illustrated. The small book should be in collections on psychiatry.

Introduction to Physiological and Pathological Chemistry. By L. Earle Arnow, Ph.G., Ph.D., M.B., M.D., vice-president and director of research, Sharp and Dohme division of Merck and Company, Incorporated, West Point, Pennsylvania, and professor of chemistry, Bryn Mawr College Summer School of Nursing, Bryn Mawr, Pennsylvania, 1941-1943 and 1945. Revised with the assistance of Marie C. D'Andrea, R.N., educational director, School of Nursing, St. Vincent's Hospital, Indianapolis. Fourth edition. 8°, cloth, 508 pp., with 108 illustrations and 28 tables. St. Louis: C. V. Mosby Company, 1953. $3.75.

In this edition a book intended for students and first published in 1939 has been revised and brought up to date. Three new chapters have been written on nuclear reactions and atomic energy, the modern periodic table in chemistry and the chemistry of the blood. There is a good index, and the publishing is excellent.

The Nursing Mother: A guide to successful breast feeding. By Frank H. Richardson, M.D. 8°, cloth, 204 pp. New York: Prentice-Hall, Incorporated, 1953. $2.95.

This small book has been written for the lay readers with the objective of increasing the employment of natural feeding by the mother.

Ophthalmologic Diagnosis. By F. Herbert Haessler, M.D., professor of ophthalmology and director, Division of Ophthalmology, Marquette University School of Medicine. 8°, cloth, 387 pp., with 151 illustrations. Baltimore: Williams and Wilkins, 1953. $8.00.

The first five chapters of this new book on diagnosis of diseases of the eye present diagnostic procedures under the headings of general survey of the patient, disturbances of functions, abnormalities in the adnexa, the anterior segment and media and fundus. The following chapters consist of a series of essays on functions, adnexa and the anterior and posterior segments. There is a good index, and the book is well published.

Differential Diagnosis of Common Diseases of the Eyeground. By Paul Tower, M.D. 4°, cloth, 243 pp., with 126 illustrations. New York, New York: Grune and Stratton, 1953. $10.00.

This new book is based on long years of teaching experience by Dr. Tower. In successive chapters he deals with the normal fundus, congenital anomalies, diseases of the retina, choroid and macula, glaucoma, diseases of the optic nerve and myopia. Lists of references are appended to the chapters. The text is well illustrated; there is a good index, and the publishing is excellent.

Vorbeugende Gesundheitsfürsorge. By Dr. Med. Wilhelm Hagen, councilor in Bundesministerium des Innern and lecturer, Friedrich-Wilhelms-Universität Bonn. 8°, paper, 131 pp. Stuttgart: Georg Thieme, 1953. DM 7.20. (Distributed by Grune and Stratton, New York.)

This monograph discusses the various aspects of personal health and hygiene, especially in relation to women and children in the Republic of Germany, as compared with Holland, Denmark, Sweden, Great Britain and the United States. The treatment of Germany is extensive. The monograph should be in all public-health collections.

Pharmakologie als theoretische Grundlage einer rationeller Pharmakotherapie. By Knud O. Møller, professor of pharmacology, Universität Kopenhagen. Second German edition. Translated and adapted from the fourth Danish edition by Dr. O. Walker, Basel. 8°, cloth, 812 pp., with 55 illustrations. Basel: Benno Schwabe and Company, 1953. Geb. Fr. 57.-

This new edition of a standard Danish pharmacology has been thoroughly revised and brought up to date. Many sections have been added, and many have been completely rewritten. There is a bibliography of 54 pages and an extensive index. The publishing is excellent.

Experimental Atherosclerosis. By Louis N. Katz, M.D., director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, and professorial lecturer in physiology, University of Chicago School of Medicine; and Jeremiah Stamler, M.D., research associate, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, and established investigator, American Heart Association. 8°, cloth, 375 pp., with 46 illustrations and 84 tables. Springfield, Illinois: Charles C Thomas, 1953. $10.50. (Publication No. 124, *American Lecture Series.*)

The authors of this extensive monograph discuss experimental atherosclerosis in detail and survey the pertinent literature. Experimental work done on the chick is described fully. There is a bibliography of 713 references and author-and-subject references. The book should be in all medical libraries and in cardiovascular collections.

Introduction to Laboratory Chemistry. By L. Earle Arnow, Ph.G., Ph.D., M.B., M.D., director of research, Sharp and Dohme Division, Merck and Company, Incorporated, West Point, Pennsylvania, and professor of chemistry, Bryn Mawr College Summer School of Nursing, Bryn Mawr, Pennsylvania, 1941-1945. Revised with the assistance of Marie C. D'Andrea, R.N., educational director, School of Nursing, St. Vincent's Hospital, Indianapolis. Fourth edition. 8°, cloth, 108 pp., with 38 illustrations. St. Louis:C. V. Mosby Company, 1953. $1.50.

This manual presents 144 experiments in the field of physiologic and pathological chemistry and is intended as a supplement to the author's book on these subjects.

ABC für Zuckerkranke: Ein Ratgeber für den Kranken. By Prof. Dr. Ferdinand Bertram, physician-in-chief, medizinischen Klinik des Allgemeinen Krankenhauses Langenhorn, Hamburg. Fifth edition. 8°, paper, 71 pp., with 5 illustrations and 10 tables. Stuttgart: Georg Thieme, 1953. DM 3.60. (Distributed by Grune and Stratton, New York.)

This is a new edition of a manual for diabetic patients first published in 1947 that has gone through five editions in the ensuing six years. The fourth edition having gone out of print, the author has revised the present edition to bring the material up to date. The text deals with dietetic and insulin treatment and physical labor and life expectancy.

Fisiopatologia e clinica della acloridria e degli stati ipocloridrici. By G. Dominici and D. Furbetta. 8°, paper, 225 pp., with 55 illustrations. Napoli: Edizioni Scientifiche Italiane, 1953. (Istituto di Clinica Medica Generale della Universitá di Perugia.)

This monograph presents a clinical physiologic and pathological study of achlorhydria and hyperchlorhydria. The authors discuss the physiology of the secretion of hydrochloric acid and the physiopathology of the two states; this is followed by chapters on pathology, diminution of the gastric secretion by agents produced in secretion, achlorhydria and pernicious anemia, achlorhydria in the digestive function and treatment. The literature is surveyed, and there is a bibliography of 23 pages.

Die Teleröntgentherapie. By Prof. Dr. W. Teschendorf. 8°, paper, 72 pp., with 8 illustrations. Stuttgart: Georg Thieme, 1953. DM 8.70. (Distributed by Grune and Stratton, New York.)

The author of this small monograph discusses the use of teleroentgentherapy for the radiation of the whole body at a single sitting, as well as of the trunk or a single region. The text is divided into two parts: general and special. The former deals with theory and technic. The latter considers the various diseases treated, including polycythemia, leukemia, lymphogranuloma, tumor metastases, prophylaxis against tumors, benign diseases and diseases of the skin. There is a bibliography of 6 pages.

NOTICES

TUFTS MEDICAL ALUMNI LECTURE

The annual Tufts Medical Alumni Lecture will be delivered at Tufts College Medical School, on Tuesday, February 16, at 11 a.m. Dr. Patrick J. Fitzgerald, professor of pathology, State University of New York College of Medicine at New York City, will speak on the subject "Radioactive Isotopes in Pathology." Physicians and students are invited.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 1 and 15, MARCH 1 and 15, APRIL 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

FEBRUARY 1–25. Consultation Clinics for Crippled Children. Page 180.

FEBRUARY 2–4. Examination for Public Health Service Medical Officers. Page 750, issue of October 29.

FEBRUARY 5 and APRIL 9. New England Society of Anesthesiologists. Page 87, issue of January 14.

FEBRUARY 5–MAY 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

FEBRUARY 8. New England Cardiovascular Society. Page 129, issue of January 21.

FEBRUARY 9. New York Society for Circulatory Diseases. Page 129, issue of January 21.

FEBRUARY 9. Harvard Medical Society. Page 129, issue of January 21.

FEBRUARY 15–20. Pan-American Academy of General Practice. Page 790, issue of November 5.

FEBRUARY 16. Tufts Medical Alumni Lecture. Page 181.

FEBRUARY 20 and 21. Mid-Winter Radiological Conference. Page 130, issue of January 21.

FEBRUARY 23–25. College of Medical Evangelists Alumni Postgraduate Convention. Page 1044, issue of December 17.

FEBRUARY 26 and 27. New England Diabetes Association. Page 129, issue of January 21.

MARCH 3 and APRIL 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

MARCH 11–13. American Orthopsychiatric Association. Page 129, issue of January 21.

MARCH 15–26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

MARCH 22–25. American Academy of General Practice. Page 129, issue of January 21.

MARCH 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

APRIL 8–11. International Academy of Proctology. Page 130, issue of January 21.

MAY 14–16. Fifti Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

MAY 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

JULY 22 and 23. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18. American Heart Association Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

MAY 12. 113th Annual Meeting. Andover Country Club, Andover.

MIDDLESEX EAST

MARCH 24.

MAY 11. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 4

THURSDAY, FEBRUARY 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

*8:15 p.m. Deaconess Medical Lecture. The Use of Fructose in Diabetes. Dr. Alexander Marble. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, FEBRUARY 5

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–5:00 p.m. Boston Lying-in Hospital Journal Club. The Prevention of Transfusion Reactions. Dr. Mark F. Lesses. The Use of Blood and Cell Fractions in Complications of Obstetrics. Dr. James L. Tullis. Auditorium, Boston Lying-in Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, FEBRUARY 6

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Auditorium, New England Center Hospital.

MONDAY, FEBRUARY 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.

8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main amphitheater, Peter Bent Brigham Hospital.

*8:00 p.m. New England Cardiovascular Society. Morse Auditorium, Museum of Science.

TUESDAY, FEBRUARY 9

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

*12:30–1:30 p.m. Medical Journal Club. Cafeteria, New England Deaconess Hospital.

*4:30–5:30 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

8:00 p.m. Harvard Medical Society. New Lecture Room, Harvard School of Dental Medicine, 188 Longwood Avenue.

WEDNESDAY, FEBRUARY 10

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Medical Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.

12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.

2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.

*5:00–6:00 p.m. American Cancer Society Telecast. Lymphomas and Leukemias. Drs. Alfred Gellhorn and Ruth Guttman. Children's Cancer Research Center, 35 Binney Street.

*Open to the medical profession.